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Addressing vitamin D deficiency in Canada: A public health innovation whose time has come

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SUMMARY

There is disturbing evidence of widespread vitamin D deficiency in many population groups, particularly within nations at high latitude. Numerous recent studies in the scientific literature associate vitamin D deficiency with a colossal increase in morbidity and mortality. Since Canada is at higher latitude, this review assesses the vitamin D status within the Canadian population. This review was prepared by assessing available medical and scientific literature from Medline, as well as by reviewing several books and conference proceedings. A standard 25(OH)D level of 75–80 nmol/l or more was used to indicate vitamin D sufficiency. Between 70% and 97% of Canadians demonstrate vitamin D insufficiency. Furthermore, studies assessing 25(OH)D levels of vitamin D at 25–40 nmol/l reveal that many Canadians have profoundly deficient levels.

Repletion of vitamin D3 with 2000 IU/day for those not receiving judicious sun exposure and those with no contra-indications would likely achieve normalized levels in more than 93% of patients, without risk of toxicity. Explicit directives regarding vitamin D assessment and management are urgently required.

Introduction

Involved in the regulation and expression of over 900 genes,[1] vitamin D (VTD) has recently been recognized as an essential hormone required for innumerable physiological processes. Despite abundant evidence that VTD inadequacy is associated with widespread and assorted health problems including many cancers, heart disease, diabetes, infectious illnesses and autoimmune disorders,[2,3] numerous studies suggest an ongoing epidemic of VTD deficiency in Canada. With little risk and minimal cost, restoration of VTD adequacy with innovative public health interventions and low-cost supplementation may have the potential to ameliorate extensive suffering and dramatically improve the health and well-being of Canadians.

As ultraviolet B (UVB) rays from sunshine are the major source of VTD production in most people, various clinical studies show that high latitudes – where UVB sunlight intensity is too weak for extended periods to induce sufficient VTD skin synthesis for many people – have a major impact on VTD production. For example, reports in the literature suggest that 26.27% of Israelis (at 32°N), 57% of study participants in Boston (at 42°N) and 61–70% of Finns (at 64°N) have 25(OH)D levels lower than 37.5 nmol/l.[4–6] Living at latitudes between 43° and

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55°N, most Canadians are at high risk for VTD deficiency. This review was designed to assess the VTD status of the Canadian population as a whole.

There is ongoing discussion in the literature regarding optimal VTD status as measured by the main circulating metabolite, 25(OH)D. It has been known for some time, that 25(OH)D levels above 78 nmol/l are required to avoid increases of parathyroid hormone,[7] and that absorption of calcium, magnesium and phosphate is maximized at values above 85 nmol/l.[8] Levels of at least 90 nmol/l are suggested for genomic stability and prevention of cancer.[9] With the existing state of knowledge, however, a cut-off value for VTD deficiency had previously been assigned as 75 nmol/l; a level that has been used in many studies. However, it has recently been suggested that ideal levels range from 100 to 150 nmol/l; values typically found in individuals with regular sun exposure living in sunny climates. Although toxicity is a distinct possibility with excessively high levels (above 250 nmol/l), the human body appears to have self-regulatory mechanisms to prevent toxicity, and thus the margin of safety is much higher than previously thought.[10]

Methodology

In this paper, an assessment of the VTD status in Canadians is performed by summarizing available published studies of 25(OH)D levels in population groups in Canada. This review was prepared by assessing available medical and scientific literature from Medline, as well as by reviewing several books and conference proceedings. Searching techniques included keyword searches with terms related to VTD and related disease. Available publications were reviewed, and incorporation of data was confined to information deemed to be of clinical significance.

After research and clinical data were compiled, information relevant for clinical practice and public health was prepared in discussion format as well as in table form, and is presented in this manuscript. Table 1 provides a review of Canadian studies to date. The format of a traditional integrated review was chosen as such reviews play a pivotal role in scientific research and professional practice in medical issues with uncharted clinical territory and innovative public health strategy.[11]

Results

Recent Canadian research using a 25(OH)D level of 72–80 nmol/l as the standard for VTD adequacy demonstrates that 70–97% of the Canadian population in various clinical settings have an inadequate VTD status[3,12–17] (Studies 1–7 in Table 1). Studies using values as low as 25–40 nmol/l as a cut-off show that 14–60% of various populations are affected[18–26] (Studies 8–16 in Table 1).

Currently, the mean 25(OH)D level in the Canadian studies in Table 1 is near 50 nmol/l in winter and 60 nmol/l in summer. In the literature reviewed, subpopulations with dark skin colour or First Nations have mean levels of 40 nmol/l. Although concerns have been expressed about the exact validity of testing with radioimmunoassay (RIA) or liquid chromatography mass spectrometry (LCMS) methodology, as was done in many of these studies, the coefficient of variability (intra- and interassay) for the RIA is approximately 9.4–12.5%[12] and for LCMS is approximately 8–9%.[27] Even at the maximum variable levels, mean winter levels are at best, 55 nmol/l and in the summer, mean levels would approach 70 nmol/l with at least 70% of people in this analysis having inadequate levels. Accordingly, there is abundant and consistent evidence of widespread VTD insufficiency in Canada. Recent research also highlights specific determinants which place individuals and groups at particular risk for deficiency.

Particular at-risk populations for VTD deficiency as outlined in the literature include non-Whites, First Nations, the institutionalized, the obese, children, pregnant women and newborns.[3,28] A recent study at latitude 53°N in Edmonton in western Canada (a latitude that includes many cities across the globe such as Moscow, Hamburg, Manchester and Warsaw) confirmed that these subcategories are at pronounced risk for VTD insufficiency, and was in agreement with previous literature in all demographic groups[3] (Table 2).

There does not seem to be much change in Canadians' VTD status of late, despite increasing media attention on the VTD issue. The most recent epidemiologic assessment of 25(OH)D levels in a large random sample of Canadians[29] confirmed widespread VTD deficiency, and the Edmonton study of 1433 patients showed almost identical results.[3] In review, there is suggestive evidence from a plethora of studies that a VTD insufficiency epidemic currently exists in Canada, with a particular problem in dark-skinned individuals, First Nations peoples, obese persons, pregnant women and the paediatric population.

Discussion

Recent reviews of the literature highlight abundant evidence confirming the plethora of benefits of achieving improved VTD levels in the adult as well as the paediatric population.[3,28] Many studies demonstrate that VTD sufficiency significantly diminishes risk for acquiring several malignancies including prostate, colon, breast, pancreatic and lung cancers.[2,3,28] The risk of assorted musculoskeletal conditions is lessened and rates of fatal stroke, hypertension, diabetes and incident cardiovascular events are also diminished with VTD adequacy.[2,3,28] Infants given 2000 IU/day had an 80% reduction of developing type 1 diabetes later in life.[30] The list of conditions that are ameliorated or obviated by achieving VTD adequacy continues to unfold, but despite sufficient evidence, the assessment of VTD adequacy is not the clinical standard of care in the Canadian medical and public health community.

Until recently, the recommended dose for VTD intake was 400 IU/day; however, evidence has generally confirmed that this dose is insufficient to optimize 25(OH)D levels in most individuals. Based on emerging research about current versus desired values, new recommendations and guidelines are beginning to emerge for supplementation in general, as well as for specific conditions. Recognizing that supplemental intake of 1000 IU VTD will raise 25(OH)D levels by approximately 25 nmol/l on average, current literature suggests that an intake of 1000 IU VTD for all adults would be required to bring VTD

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Table 1 – Studies on vitamin D status in the Canadian population.

Study name	25(OH)D value used as cut-off for deficiency or estimated adequate intake	Targeted group	Comments and percentage of people (i) below designated cut-off value (ii) mean 25(OH)D level (when available)
1. VTD status of clinical practice populations at higher latitudes: analysis and applications[3] $n = 1433$	80 nmol/l	Three clinical practice settings	(i) 68.75% of overall sample had levels <80 nmol/l (ii) 80% age 19 years or less <80 nmol/l (iii) 81% First Nations and 76% pregnant women <80 nmol/l *Mean 25(OH)D levels (nmol/l)* Spring 63.84 (SD 28.64) Summer 71.27 (SD 25.69) Autumn 73.95 (SD 29.03) Winter 66.10 (SD 30.56) * see Table 2 for other parameters and mean VTD levels
2. VTD insufficiency in a population of healthy western Canadians[12] $n = 63$	80 nmol/l	Levels were taken once each season	(i) 97% had at least one level <80 nmol/l during the year (ii) 68% had levels <80 nmol/l in summer *Mean serum 25(OH)D (nmol/l)* Winter 57.3 (SD 21.3) Spring 62.9 (SD 28.8) Summer 71.6 (SD 23.6) Autumn 52.9 (SD 17.2)
3. Low wintertime VTD levels in a sample of healthy young adults of diverse ancestry living in the Toronto area: associations with VTD intake and skin pigmentation[13] $n = 107$	75 nmol/l	Non-European adults	(i) 93% of total population had levels <75 nmol/l (ii) 75% had levels <50 nmol/l Skin pigmentation correlated inversely with VTD level *Mean 25(OH)D nmol/l* Overall 39.4 (15.3, 77.1) East Asian subpopulation 34.5 (15.1, 71.5) European subpopulation 55.9 (26.7, 96.3) South Asian subpopulation 30.5 (13.3, 51.6)
4. Low VTD status in a representative sample of youth from Quebec, Canada[14] $n = 1753$	75 nmol/l	Children and adolescents aged 9, 13 and 16 years	93% had levels <75 nmol/l 25(OH)D levels decreased with (i) age in both males and females and (ii) increasing body mass index in girls *Mean 25(OH)D from January to May 1999* **Boys** / **Girls** Age 9 (51.5) $n = 284$ / Age 9 (48.6) $n = 275$ Age 13 (43.9) $n = 293$ / Age 13 (41.3) $n = 249$ Age 16 (42.7) $n = 305$ / Age 16 (47.3) $n = 347$
5. Seasonal variation of maternal serum VTD in Newfoundland and Labrador[15] $n = 593$ (maternal levels in summer and winter)	75 nmol/l	Uniformly random sample	(i) 89% had levels <75 nmol/l in winter (ii) 68.6 had levels <75 nmol/l in summer 1.7% had levels <25 nmol/l in summer 6.6% had levels <25 nmol/l in winter *Mean 25(OH)D level (nmol/l)* Winter 52.1 ($n = 304$) Summer 68.6 ($n = 289$) SD not supplied

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Table 1 (*continued*)

Study name	25(OH)D value used as cut-off for deficiency or estimated adequate intake	Targeted group	Comments and percentage of people (i) below designated cut-off value (ii) mean 25(OH)D level (when available)
6. VTD insufficiency and treatment with oral VTD_3 in northern-dwelling patients with chronic kidney disease [16] $n = 128$	75 nmol/l	Prospective controlled trial Intervention group with stage 3–5 kidney disease	(i) 45% had levels <37.5 nmol/l (ii) 93% had at least one level <75 nmol/l *Mean 25(OH)D level (nmol/l)* Control group $n = 63$, 54 (SD 24) Vitamin D supplementation group (with chronic kidney disease) baseline $n = 65$, 40 (SD 14) Intervention with 1000 IU only reduced insufficiency by 37%
7. VTD insufficiency common in newborns, children and pregnant women living in Newfoundland and Labrador[17] $n = 149$	75 nmol/l	Cross-sectional analysis	(i) 77.1% of children <75 nmol/l (ii) 78.0% of maternal blood <75 nmol/l (iii) 82.4% of cord blood <75 nmol/l *Mean 25(OH)D level (nmol/l)* Children — Winter 52.6 ($n = 24$); Summer 67.7 ($n = 24$) Maternal blood — Winter 51.9 ($n = 25$); Summer 61.9 ($n = 25$) Cord blood — Winter 48.6 ($n = 24$); Summer 63.3 ($n = 27$)
8. Prognostic effects of 25(OH)D levels in early breast cancer[18] $n = 512$	72 nmol/l	Prospective inception cohort study	(i) 37.5% had levels <50 nmol/l defined as deficient (ii) 38.5% had levels between 50 and 72 nmol/l defined as insufficient (iii) 24% had levels above 72 nmol/l *Mean 25(OH)D level (nmol/l)* All participants: 58.1 (SD 23.4)
9. Intake of calcium and VTD in three Canadian long-term-care facilities[19] $n = 53$	Adequate intake of residents by dietary assessment	Nursing home patients (mean age 86 years)	74% did not achieve adequate VTD (>600 IU of VTD) intake from diet alone Mean 25(OH)D was not available
10. Seasonal prevalence of VTD deficiency in institutionalized older adults[20] $n = 155$	40 nmol/l	Institutionalized patients, mean age 83.2 years	(i) 60% had levels <40 nmol/l in winter and 38% in summer (ii) 18% had levels <25 nmol/l in winter and only 9% in summer *Mean 25(OH)D (nmol/l)* Spring 39.9 (SD 19.7) Autumn 44.9 (SD 16.9)
11. Are national VTD guidelines sufficient to maintain adequate blood levels in children?[21] $n = 90$ (patients between 2 and 16 years of age	40 nmol/l	Consecutive patients in emergency department in April 2003. Cross-sectional study	(i) 6% of the population had deficiency (<25 nmol/l) and 34% were insufficient (<40 nmol/l) (ii) 9–16-year-old boys and girls: 69% of boys and 35% of girls had levels <40 nmol/l (iii) 2–8-year-old boys and girls: 22% of boys and 8% of girls had levels <40 nmol/l *Mean 25(OH)D level (nmol/l)* All participants: 47.2 (SD 14.6)

12. Wintertime VTD insufficiency is common in young Canadian women, and their VTD intake does not prevent it[22] $n = 796$	40 nmol/l	Younger women (age 18–35 years)	(i) 14.8% of white women had levels <40 nmol/l (ii) 25.6% of non-White, non-Black women had levels <40 nmol/l *Mean 25(OH)D level (nmol/l)* White 58 (SD 24) Non-White 51 (SD 22) Black 68 (SD 40)
13. Frequency of VTD deficiency in adults with Crohn's disease[23] $n = 242$	40 nmol/l	Consecutive patients enrolled in prospective longitudinal study	Overall: (i)8% had levels <25 nmol/l (ii)22% had levels <40 nmol/l Seasonal variation: 2.8% had levels <25 nmol/l in summer 11.9% had levels <25 nmol/l in winter Mean 25(OH)D level (nmol/l) was not declared
14. Canadian Aboriginal women have a higher prevalence of VTD deficiency than non-Aboriginal women despite similar dietary VTD intakes[24] $n = 255$	37.5 nmol/l	Urban and rural Aboriginal women and urban White women	32% of rural Aboriginal, 30.4% of urban Aboriginal and 18.6% of urban White women were deficient in VTD with levels <37.5 nmol/l *Mean 25(OH)D level (nmol/l)* Rural Aboriginal 41.8 (SD 14.5, $n = 26$) Urban Aboriginal 53.8 (SD 25.5, $n = 284$) Urban White 68.6 (SD 32.1, $n = 146$)
15. Perinatal VTD and calcium status of northern Canadian mothers and their newborn infants[25] $n = 121$ pairs (mother and child)	30 nmol/l	Circumpolar Caucasian and First Nations	6% of mothers and the majority of infants had levels <30 nmol/l, >90% had levels <75 nmol/l *Mean 25(OH)D level (nmol/l)* Caucasian 59.8 (SD 29.4) Indian 52.1 (SD 25.9) Inuit 48.8 (SD 14.2)
16. VTD deficiency in a Manitoba community[26] $n = 160$	25 nmol/l	Mother–child pairs in a northern community	(i) Mothers: 76% had levels <25 nmol/l Mean 25(OH)D: 19.8 nmol/l (ii) Children: 43% had levels <25 nmol/l Mean 25 (OH)D: 26.2 nmol/l
17. Statistics Canada: VTD (nmol/l) plasma concentrations by age and gender household population, Canada, 2007–2008[27] $n = 2673$ (1277 male, 1296 female)	No cut-off New data	Random sample	*Mean 25(OH)D level (nmol/l)* Both genders 66.9 ($n = 2673$) Male 65.7 ($n = 1277$) Female 68.0 ($n = 1396$) SD not supplied Age group 20–39 had the lowest mean 25(OH)D level of 63.5 nmol/l

VTD, vitamin D; SD, standard deviation.

Table 2 – Mean vitamin D levels by various parameters as found in one Canadian study in nmol/l.[3]

Parameter	Categories	*n*	Mean	SD
Age	Paediatric	87	60.78	33.04
	Young adult	172	67.27	31.45
	Middle adult	754	64.93	26.94
	Senior	420	76.44	28.86
Gender	Male	370	68.95	27.34
	Female	1063	68.12	29.50
Skin tone	Dark	18	50.67	27.87
	Midcolour	185	64.11	31.24
	Light	1179	69.35	28.07
	First Nation	33	52.18	35.61
Pregnant	No	977	68.55	29.42
(females only)	Yes	83	61.83	29.52
Body mass	Underweight	33	62.55	33.44
index category	Normal	322	67.23	28.79
	Overweight	217	69.43	29.93
	Obese	132	60.10	26.08
Season	Spring	435	63.84	28.64
	Summer	299	71.27	25.69
	Autumn	324	73.95	29.03
	Winter	373	66.10	30.56
Glasses of milk	0	713	65.28	29.09
per day	1–2	492	67.86	28.67
	>2	206	77.16	26.37
Fish servings	0	742	64.64	28.21
per week	1	465	71.06	29.10
	>1	203	72.87	28.97
Fish oil supplement	No	1074	63.81	28.38
(cod liver oil)	Yes	337	80.97	26.25
Vitamin D	None	714	56.64	25.30
supplement	50–400 IU	487	73.23	24.71
	>400 IU	210	93.91	28.68
Recent sun exposure	Minimal	878	63.21	27.98
	Moderate	362	72.34	26.70
	Lots of sun	171	82.68	31.03
Tanning bed use	None	1279	66.01	27.85
	Sometimes	109	84.54	29.40
	Regular use	23	94.74	40.11

SD, standard deviation.

concentrations up to 75 nmol/l in no less than 50% of the population.[31] Evidence in another Canadian study, however, suggests that daily supplementation with 2000 IU of VTD_3 would replete approximately 93% of patients without risk of toxicity (except in individuals with both regular tanning bed use and significant sun exposure).[3] Another recent study in a nursing home population of Canadians demonstrated that 94.1% of nursing home residents had a $25(OH)D_3$ level in excess of 80 nmol/l after a minimum of 5 months of daily 2000 IU VTD_3 supplementation.[32] The Canadian Pediatric Society has recommended that, pregnant women should ingest VTD 2000 IU/day to secure adequacy during the gestational period,[33] and the Canadian Cancer Society has suggested 1000 IU in winter months or all year long if there is lack of sun exposure in the summer months.[34]

There is also much discussion worldwide on appropriate dosing required for optimal VTD status. The Vitamin D Action Consortium of Scientists, is calling for a standard VTD intake of 2000 IU/day in much of the world with the hope of achieving levels of 100–150 nmol/l (40–60 ng/ml) in most individuals.[35] Some groups, such as the American Pediatric Society, have been reluctant to embrace a huge rise in recommended VTD intake. Based on recent findings about rickets, they have suggested a modest increase from 200 IU/day to 400 IU/day in children in order to prevent or overcome rickets; a problem still being reported in the American population.[36] Some groups, however, are beginning to look beyond isolated conditions such as rickets as research continues to emerge that higher dosing may have public health benefits for many other conditions, including recent information on the impact of an optimal VTD status on immune function.

Vitamin D dosing and innate immune function

A well-functioning immune system is recognized as a prerequisite for health; impaired immunity predisposes individuals to various infections and carcinogenic processes that threaten and endanger human health and wellness. Adequate VTD in the form of $25(OH)D_3$ is required as a substrate for the formation of activated VTD [$1,25(OH)_2D_3$] for the production of cathelicidins; a fundamental component of a healthy immune system.[37] Cathelicidins act as inherent antimicrobial peptides required for antimicrobial activity against various infections such as, for example, tuberculosis (TB).[38]

TB has recently become a leading infectious disease and public health threat in the world, accounting for considerable morbidity and mortality, particularly in developing nations. In decades gone by, sun exposure was always considered part of the treatment of TB. It is now recognized that daily sun exposure accounts for the innate production of 10,000–20,000 IU of VTD; a process achieved in a relatively short period of time. To confirm the efficacy of sun exposure on the course of TB, a recent study showed that using 10,000 IU of daily VTD_3 in addition to antibiotic treatment resulted in a 100% sputum conversion rate to negative. Those using the antibiotics alone experienced a 23% failure rate in sputum conversion.[39] However, suboptimal dosing of VTD fails to provide this necessary immune protection. For example, a randomized controlled trial using three 100,000 IU doses in months 1, 5 and 8 (a dose that would translate into less than VTD 1000 IU/day) showed no difference in the control or treatment group in rates of sputum conversion in TB-exposed patients.[40] More studies are required to clarify the specific dose and the serum 25(OH)D level required for successful treatment of individual conditions. Research to date confirms that adequate VTD is required for optimal innate immune functioning.

Comparative impact on public health

In order to recognize the potential impact of a strategy designed to address the VTD issue in Canada, it is valuable to compare this proposed endeavour with other contemporary public health undertakings. With recognition that colorectal cancer has become the second leading cause of cancer death in many parts of Canada (lifetime incidence of approximately one in 19 Canadians), a concerted public health effort has been employed to address this challenge.

Early diagnosis and aggressive intervention have proven to be of benefit with regards to increasing survival for those with colorectal cancer. To secure early diagnosis, the benefits of annual screening measures to identify this disease are being

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promoted to the public through media advertising. Furthermore, various educational initiatives directed at the medical community seek to achieve widespread annual screening for this disorder. Comparable with an annual Pap smear, yearly screening for possible bowel tumours is increasingly being recommended as the clinical standard of care.

The purported claims of diminished morbidity and mortality are based on projected findings that early detection by a national bowel cancer screening programme would provide early discovery of many tumours, and reduce colorectal cancer mortality in those screened by 13–15% over the next 20 years[41]; a figure considered to be of major significance when applied to a large-scale population. The projected cost savings are enormous and the potential to abet those with a diagnosis of colorectal cancer and to prevent premature death is evident.

A comprehensive public health approach to diminishing human suffering associated with colorectal cancer, might include a similar concerted effort to optimize VTD levels in the population. Considering that a prospective study of colon cancer risk based on levels of 25(OH)D in more than 25,000 participants resulted in a 75–80% reduction in risk for developing colon cancer for those with higher levels compared with those with low levels,[42] incorporation of a VTD strategy may be eminently sensible, with potential outcomes that far exceed any cancer screening programme. The immense cost savings, as well as the opportunity to completely preclude colorectal cancer in many people with the associated reduction in morbidity and mortality, behooves the medical community to pursue a VTD optimization programme.

Comparative potential public health impact can also be considered in relation to breast cancer. With a lifetime incidence of one in every eight women, breast cancer is the most frequently diagnosed cancer among women in Canada. Screening for this lesion through regular mammography is practised within many jurisdictions because of evidence that mammograms identify breast cancer at earlier stages and thus reduce breast cancer mortality. In women who have had mammographic screening compared with those in control groups, mortality reduction is approximately 20–35% for women over 50 years of age[43] and approximately 21% in women aged 40–49 years.[44] Despite widespread screening, however, breast cancer still remains the second leading cause of cancer-induced death, and repeated mammography carries a small but cumulative risk of adverse radiation to the breast.[45]

At the same time, however, the literature has identified VTD as an effective, non-invasive, inexpensive intervention which lacks risks at recommended doses, and has the potential to diminish the risk of acquiring breast cancer by at least 50%.[46] Furthermore, there is a recognized and significant improvement in prognosis for those diagnosed with early breast cancer who subsequently achieve sufficient VTD status.[18]

Finally, the impact and cost savings in relation to optimizing VTD status and cancer prevention in general are evident from a recent study. A prospective double-blind, randomized placebo-controlled research study investigating cancer incidence in postmenopausal women supplementing with VTD and calcium found a 77% reduction in risk of all-cancer incidence 2–5 years after commencing supplementation.[47] Such an outcome has the potential to achieve results that are far and beyond any other screening measure for cancer in women in current use. In fact, a recent article predicted that the economic cost savings of normalizing VTD in the Canadian population would be at least 14 billion Canadian dollars per year.[48] There is abundant evidence in the scientific literature to confirm that a major public health initative to optimize the VTD status in the Canadian population would be cost-effective, without significant risk and would provide enormous benefit to the Canadian people and the sustainability of the public healthcare system.

Controversies in vitamin D research studies

In order to present a balanced perspective, it is important to note that not all studies have demonstrated benefit with VTD supplementation. Furthermore, some publications have commented on the potential danger of toxicity associated with widespread use of VTD. How does one account for the inconsistency in studies?

As only VTD 400 IU/day is required to reverse rickets, some have assumed that 400 IU is the required daily dose for prevention of VTD-related illness. As a result, this level has often been adopted as the daily requirement for the general population in many jurisdictions.[36] Subsequent studies assessing the value of VTD supplementation for other medical conditions, such as osteoporosis, have shown that this bone condition has failed to respond to 400 IU VTD,[49] and higher doses such as 800 IU/day have also failed to show a consistent benefit.[50] In response to such findings, some have concluded that VTD supplementation is not of benefit in osteoporosis or for other conditions because of similar negative outcomes. The net result is that some suggest that VTD therapy has limited, if any, benefit beyond controlling rickets.

With abundant evidence-based support from the peer-reviewed scientific literature, however, the authors of this paper and many other researchers have suggested that the inconsistent and negative results are generally the result of inadequate VTD dosing for specific conditions. Just as a grossly insufficient dosage of insulin would fail to control marked elevations of blood sugar in a type 1 diabetic, a grossly insufficient dosage of VTD is insufficient to carry out required physiological processes. One would not conclude that insulin is useless as a therapy for diabetes if insufficient doses were used; similarly, one should not conclude that VTD therapy is useless if insufficient dosing is used. This contention emphasizing the need for adequate dosing is repeatedly supported by innumerable accounts in the literature of the major health benefits that are realized when sufficient dosing is used to achieve levels of 25(OH)D that confirm sufficiency.[2,3]

There has also been debate about different VTD formulations. 25(OH)D levels can be repleted with use of either VTD_2 (ergocalciferol) or VTD_3 (cholecalciferol). VTD_2 originates from chemical synthesis or from some fungi and invertebrates; VTD_3, on the other hand, can be synthesized but is originally made in human skin and found in vertebraes and backboned fish. In addition, VTD_3 can also be extracted naturally from oils on sheep wool. These two forms of VTD are not equivalent and it appears that ergocalciferol is only one-third as potent in humans compared with cholecalciferol,[51] which explains some of the limited efficacy of VTD_2. Although they appear to be equally well absorbed, the pharmacokinetics of VTD_2 and VTD_3

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differ substantially in that cholecalciferol levels do not drop off quickly like ergocalciferol after a single dose. Furthermore, there are case reports indicating that ergocalciferol may increase insulin resistance in studies on Asians,[52] while this does not appear to be the case with cholecalciferol.[53] Much more research is needed regarding the various forms of VTD and their impact on human health. The studies demonstrating consistent clinical benefit, however, appear to use VTD_3.

Toxicity from supplementation with VTD has also been reported rarely in the literature as a potential concern associated with VTD supplementation. In fact, death has occurred as a result of excessive ingestion of large doses.[54] Scrutiny of the data confirms, however, that toxicity associated with supplementation is usually due to accidental ingestion of veterinary VTD concentrate,[55] error in VTD product formulation,[56,57] or improper mixing of VTD in milk.[58] Such infractions and the resulting extreme elevation in 25(OH)D levels can lead to nausea, vomiting, constipation, fatigue, laboratory evidence of hypercalcaemia, increased 1,25 dihydroxyvitamin D and subsequent renal failure with death in rare cases. Just as with other therapies such as insulin, toxicity is a distinct possibility with excessively high levels, but the human body appears to have self-regulatory mechanisms with VTD to prevent toxicity, and thus the margin of safety is considerably higher than previously thought.[10] A recent review has shown, that the upper limit of safe tolerability may be a dose as high as 10,000 IU/day for many consecutive months.[59]

It is important to note that just as many other therapies have cautions, there are also contraindications to VTD use, as discussed in the literature. These include use of VTD supplementation in situations of hypercalcaemia such as with sarcoidosis,[60] metastatic bone disease,[61] and conditions that have disordered VTD metabolism in activated macrophages such as Crohn's disease (active phase).[62] Unusual syndromes in children, such as William's syndrome, may also predispose individuals to develop hypercalcaemia.[63] Patients that regularly frequent tanning salons also need to be monitored as they have a propensity to develop high 25(OH)D values as a result of the ultraviolet waves used in the artificial tanning process, especially when consuming added VTD supplementation. Monitoring of 25(OH)D levels should always be performed in cases of concern.

Concluding thoughts

A review of the available medical literature suggests that most Canadians have VTD insufficiency, with a considerable proportion of the population sustaining a severe deficiency. Rather than a spurious finding in one report, VTD inadequacy has been discovered repeatedly in various subpopulations within the country, and appears to be a consistent finding in all the population studies performed thus far in Canada.

Based on considerable evidence in the literature, innovative public health recommendations regarding VTD production and intake should be pursued. A few suggestions are provided for consideration:

- Routine clinical and public health recommendations to achieve solar abstinence and to regularly use complete sun block need to be re-evaluated; judicious sun exposure assists in normalizing VTD levels and provides other beneficial effects to the human body.[64]
- Broad-based public awareness campaigns to increase awareness of the VTD problem – similar to public awareness campaigns about pandemic planning – will create an expectation of VTD assessment and intervention.
- Health practitioners should be provided with clear clinical practice guidelines regarding VTD assessment and intervention. As medical history repeatedly demonstrates that incorporation of new knowledge into clinical practice is usually a slow process, explicit directives regarding VTD assessment and management are urgently required.
- Education about nutritional biochemical requirements and nutritional status testing including assessment and management of VTD status should be a fundamental component of medical education.[65]

In Response to emerging VTD research, public health interventions have the potential to facilitate knowledge translation in order to provide better health for Canadians and other populations at similar geographic latitude. Normalization of VTD values in the Canadian population to address the current situation of widespread VTD insufficiency would yield satisfying outcomes in both the short and long term, as well as having enormous benefits for the public healthcare system.

Ethical approval

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Competing interests

None declared.

Box 1 Public health recommendations regarding VTD_3 use in Canada

1. Patients without regular sun exposure and who have no contraindications should be counselled to supplement with VTD_3 2000 IU/day. Summer sun exposure in northern latitudes may reduce requirements for supplementation to 1000 IU/day from May to September.
2. At-risk individuals should have a 25(OH)D assessment as some individuals will require more than 2000 IU/day to achieve optimal levels.
3. As the half-life for VTD is approximately 3–4 weeks, 25(OH)D measurement should be reconsidered after 4 months of supplementation in at-risk cases.
4. Exceptions for use of supplemental VTD include those with disorders associated with hypercalcaemia, such as sarcoidosis and some malignancies.

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