Vitamin D is Essential for Optimal Health: Are You Getting Enough?

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The information herein is for educational purposes only and is not to be taken as medical advice; please consult a healthcare professional for personal advice.

Fellow Canadians,
Let us make a significant improvement in our collective health and save our country billions of dollars annually by simply paying attention to our vitamin D sufficiency. Please do the following:

- Read the Abstract below and the full document if possible.
- Consider if you are vitamin D sufficient or if supplementary vitamin D is advisable for you, your family and your friends.
- Discuss vitamin D testing and sufficiency with your doctor, nurse or other healthcare providers.
- Contact the following with your vitamin D concerns: your local public health officer, provincial public health officer, provincial MP/MLA, federal MP, and any others who would benefit from your educating them.
- Request that vitamin D testing be covered by provincial health plans to help citizens take appropriate doses of vitamin D.

Abstract

Multiple studies have shown most Canadians have insufficient body levels of vitamin D (VitD, the sunshine vitamin) to ensure optimal health. The primary reason for this is inadequate exposure to sunlight's ultraviolet (UV) rays because of our northern location and indoor work, although genetics, diet, skin pigmentation, clothing, sun screen use, air pollutants, age and other factors also contribute to VitD insufficiency.

Low VitD levels are strongly associated with a broad spectrum of diseases that hamper our enjoyment of good health. Examples of these diseases include: cancers, cardiovascular disease, diabetes, viral and bacterial infections, multiple sclerosis, dementia, other neurological disorders, and poor oral health.

The fundamental importance of VitD is demonstrated by the location of specific receptors for this essential vitamin in virtually every type of human cell, where they regulate hundreds of cellular processes to maintain good health.

Evidence now shows that the amount of VitD needed to ensure bone health is lower than that required for optimal function of its many other actions. Thus, we recommend that citizens evaluate their own VitD sufficiency and consider supplementation as necessary. While Health Canada's suggested daily dose for bone health ranges from 400 to 800 IU/day, many researchers, doctors and health associations advocate much higher daily doses.

Evidence indicates that the Canadian population would be significantly healthier if it were to become VitD sufficient. Moreover, the annual savings to healthcare costs would exceed $23 billion (~6-7% of total healthcare spending in Canada for 2023, estimated to be $344 billion).

Introduction

At the Canadian Citizens Care Alliance, we believe that our healthcare "system" requires urgent attention. It does not just need more money, it requires a change in thinking from the healthcare providers and administrators. But more importantly it requires changes in the attitudes and actions of Canadians. Instead of a sickness care paradigm, Canadian Health needs to focus on wellness and health maintenance. More of the responsibility should be shouldered by individual citizens and less by healthcare professionals and hospitals. We will always need our professionals and hospitals, but we now need more active participation by the public. For some members of the public, there is no choice because many do not have access to doctors and nurses. The minimum that government must do for such unfortunate citizens is empower them to help themselves.

Changing the focus to individual responsibility of health maintenance is a step whose time has come. With an increased population of seniors, we also see a change in the type of care required to prevent and treat diseases such as cancer, cardiovascular problems, diabetes mellitus Type 2 (DM2) and dementia. Society should embrace the roles of lifestyle and nutrition to deal with chronic diseases. We must not miss the opportunity to decrease healthcare costs by foregoing an investment in health maintenance.

Let us consider just diabetes for a moment: some experts consider that 90% of DM2 cases could be prevented by lifestyle and nutrition intervention. To make matters worse, we are trending the wrong way - the incidence of DM2 is increasing by 3.3 percent per year rather than decreasing. About 29% of Canadians are now living with prediabetes or diabetes, and DM2 can reduce life expectancy by up to 10 years.

We know that calling for a change in behaviour is a big ask for our population but we have to try. We suggest that positive unifying methods be employed; thus, the message should be about improving our personal health and that of family, friends and neighbours. For personal motivation, we might consider taking advantage of technologies like continuous glucose monitors; seeing one's glucose respond to meals is surely to be motivation for some people.

Herein, we advocate facilitating individual self-help by encouraging personal sufficiency in VitD as a good place to start.

Canadians have Insufficient Vitamin D for Optimal Health.

Evidence has accumulated over decades that our vitamin D (VitD) status is significantly below optimal. For example, Schwalfenberg *et al.* (2010)[1] published a review entitled, "*Addressing vitamin D deficiency in Canada: A public health innovation whose time has come*." For definitions of deficient and insufficient, they used modest standards. VitD levels with less than 25-40 nanomoles/litre (nmol/L) (*i.e.,* 10-16 nanograms/millilitre (mL); 1 nanogram is 1 billionth of a gram) were considered as deficient and less than 72-80 nmol/L were considered as insufficient. Even employing these older standards, they concluded that 70-97% of Canadians were VitD insufficient, and 14-60% were clearly deficient. In the last decade, the field has continued to advance with many clinicians and scientists raising their criteria for sufficiency; this has the effect of making Schwalfenberg's team assessment of one's VitD status look even worse. This was not Schwalfenberg's first attempt to get the attention of the Canadian medical community; he published a clinical review, entitled "*Not enough vitamin D- Health consequences for Canadians*" in the journal Canadian Family Physician back in 2007.[2] If Canada had heeded his advice at that time, the health of Canadians and our healthcare system would far better off today. Let us just assume for now that Canadians and residents of many other northerly countries have a serious lack of VitD. This was confirmed by Cui *et al*. (2023)[3] in their review entitled, "*Global and regional prevalence of vitamin D deficiency in population-based studies from 2000 to 2022: A pooled analysis of 7.9 million participants*."

Why is There a Shortage of Vitamin D?

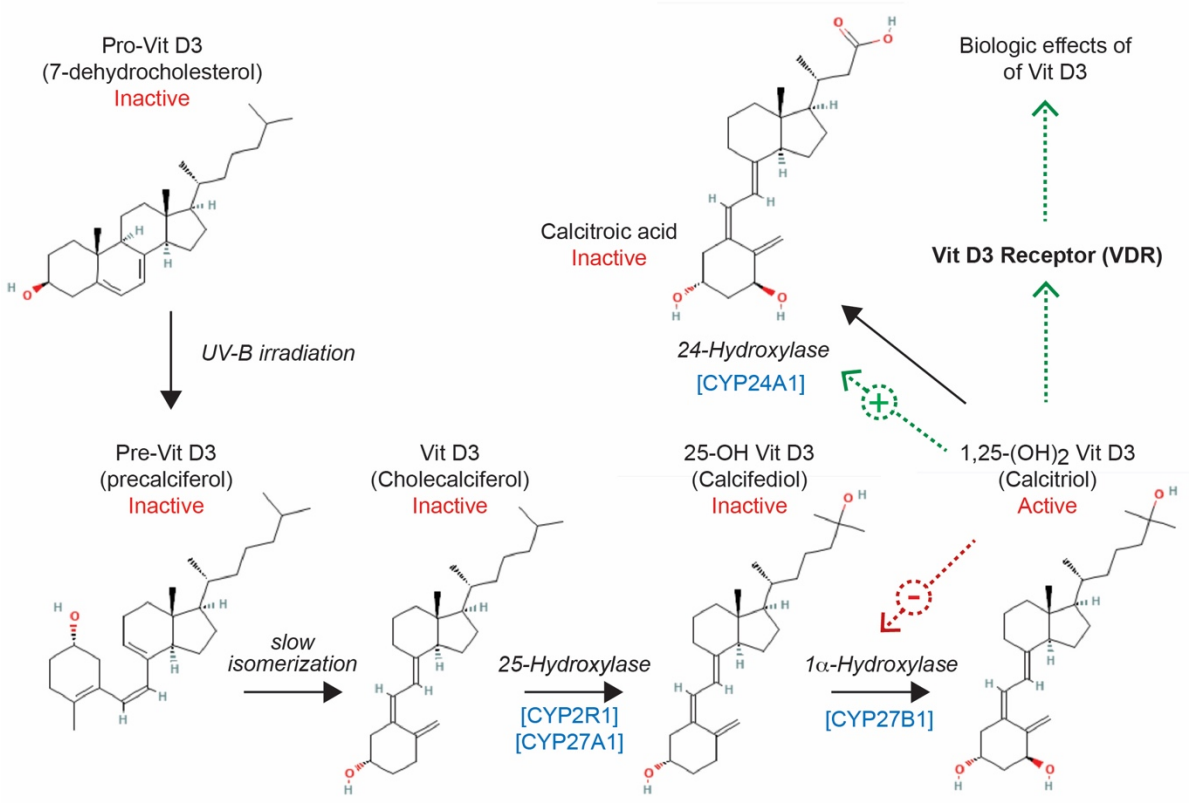
Remember, VitD is called the "sunshine vitamin" for a very good reason. When the cholesterol precursor of VitD, 7-dehydrocholesterol, is exposed to UV-B rays in the skin, VitD3 is created. Knowing this, it is not a hard stretch to imagine that we make more VitD3 during the summer and our skin makes little or no VitD3 during the winter, as shown in a Slovenian study by Hristov *et al.* (2020).[4] The further north we live, the less VitD we make and the more clothing we need during colder months ensures that our skin is exposed to little UV-B. In practice, Canadians have less VitD on a seasonal basis than our southerly neighbours and liberal use of sun block during the summer just further exacerbates the shortage of this vitamin.

Vitamin D does Much More than Support Bone Health.

Nowadays, we do not see a lot of weakened and bent bones in our children. Maintenance of bone health was the primary reason that VitD supplementation was encouraged in products like milk and cereals.

However, it is not quite that simple. While it is true that the weakened and bent bones of Rickets were documented during the 1600s, it was not until 1924 that VitD was identified as the product of sunlight shining on the skin. And now, VitD is considered to be a pro-hormone (or precursor) that has numerous effects throughout the human body. With the work of many different laboratories, we now know that in the skin 7-dehydrocholesterol is made into $VitD_3$ (cholcalciferol), which is then converted to calcifediol (aka 25-OH-$VitD_3$, calcidiol) in the liver and then to calcitriol (1,25-$(OH)_2VitD_3$) in the kidney. Thus, $VitD_3$ is the hormone precursor, and calcitriol is the active hormone. The latter acts through a VitD receptor, VDR (Figure 1). The circulating levels of 25-OH-VitD3/calcidiol in blood are used to determine VitD sufficiency.

Figure 1. Vitamin D metabolism.



Moreover, Jones (2008) provides the following pharmacokinetic information, "*The lipophilic nature of vitamin D explains its adipose tissue distribution and its slow turnover in the body (half-life approximately 2 mo). Its main transported metabolite, 25-hydroxyvitamin D(3) [25(OH)D(3)], shows a half-life of approximately 15 d and circulates at a concentration of 25-200 nmol/litre, whereas the hormone 1alpha,25(OH)(2)D(3) has a half-life of approximately 15 h*." [5] A longer half-life indicates slower turnover and that VitD takes time to be activated. This explains why it takes several days to see the therapeutic effects of VitD after it has been taken.

The concept of the nuclear receptor for VitD3 (VDR) is the next interesting aspect of this story. VDR was discovered in 1969, and subsequently has been found in many cells beyond those involved with the disposition of calcium. VDR is located in almost every cell in the human body where it mediates hundreds of different actions including the direct regulation of over 1000 genes. VDR is present in cells within all major organ systems - intestine, kidney, cartilage, bone, pancreas, hair follicles, epithelium, endothelium, vascular smooth muscle, cardiomyocytes, and immune cells such as leukocytes. When calcitriol enters a cell, it binds to the VDR, which then triggers a chain reaction of events. This results in the activation of some genes and the suppression of others. Some examples of genes that are activated are those for immune-related genes such as *CD14*, and *NOD2*, which are the first receptors to recognize invading pathogens, as well as genes for cathelicidin and β2 defensin, peptides with antimicrobial and antiviral activity. Examples of suppressed genes include those for interferon-gamma, which drives cellular immunity, and hepcidin, a master regulator of iron homeostasis.

What is the Scope of Vitamin D_3 Effects?

There are VDR's almost everywhere in the human body, indicating the wide breadth of VitD functions. In the face of VitD insufficiency, there will be suboptimal health seen as exacerbations of diseases of various organs/tissues. As already mentioned, Ricketts (lack of bone health) is well known but there are many others as described in the reviews by Grober *et al*. (2013)[6] and Maretzke *et al.* (2020).[7] For the present argument, we suggest considering diseases that affect major portions of Canadian society and using numbers for the leading causes of death as a guide.

Leading causes of death in Canada in 2021[8]

- Cancers – 26.6%
- Heart disease – 17.7%
- Accidents – 6.2%
- COVID-19 – 4.6%
- Stroke – 4.3%
- Chronic lower respiratory diseases – 3.5%
- Diabetes – 2.4%

Of these seven groupings, only accidents stand out as being unrelated to inadequate VitD. **Appendix I** provides more detail on each target condition.

Should We Supplement the Population with Vitamin D?

By supplementing with VitD, we anticipate significant reductions in the healthcare load attributed to the above conditions. A study published in 2021 for the UK, which has similar VitD challenges as Canada, revealed that "*increasing levels in serum 25(OH)D were independently associated with a decreased risk of all-cause and cause-specific mortality*."[9] The measurement of serum 25(OH)VitD is the usual manner of estimating VitD status.

To provide optimal health for Canadians, an important step is ensuring VitD sufficiency for all the functions listed above. This means raising the bar above the amount required for bone health. The evidence currently available for immune health indicates a target of 125-150 nmol/L, which is usually attained with a daily dose of 3000-5000 IU, compared with the dose suggested for bone health of 600-800 IU/day (Health Canada). This begs the questions as to the target for other potential beneficial effects of vitamin D sufficiency. We think that these values should be sought but we should not wait to act until we have full gold-standard studies. The benefit-to-risk ratio for infections alone is sufficient to support ensuring sufficiency of VitD in the population especially since the toxicity levels of VitD are much less of a concern than previously considered as described below.

Caveats.

Not all people will benefit from VitD supplementation because some are VitD sufficient and do not require additional doses of this nutrient. Accordingly, some participants in clinical studies did not show a health benefit of VitD supplementation; by corollary, those who are most deficient are likely to benefit most. Also, some people will be genetically predisposed to having low VitD levels, even with supplementation, while others may have comorbidities affecting liver or kidney function; for these individuals, a different form of VitD may be required to ensure adequate levels of bioactive calcitriol are reached.

In several studies, especially where a rapid response was sought, VitD treatment was found to be ineffective; we suggest that the active form, calcitriol, should have been given. Accordingly, Entrenas Castillo *et al.* (2020) observed less morbidity and mortality when they treated a viral illness (COVID-19) with calcidiol, a hydroxylated metabolite of $VitD_3$.[10]

Requirements for Vitamin D_3.

Because $VitD_3$ is made by exposure to sunlight, we are most sufficient during the summer. But there are many other variables that determine the levels of circulating VitD. These include skin area exposed, skin colour, duration of exposure, use of sun block and more. Vitamin D is also available following consumption of especially fatty fish and fish oils, red meat, egg yolk, mushrooms, fortified products such as cereals, cow and plant-based milks. For these reasons, it is a priority to invest in lab testing for individual VitD levels (tested as calcidiol). Mid-summer and mid-winter may be appropriate times to determine maximum and minimum levels, respectively. Note that VitD is fat soluble, and if supplements are used, these should be taken with food containing lipids to improve absorption.

The cost of VitD testing ranges from $32 to $93 across Canada. With some ingenuity and efficiencies of scale, the cost should be considerably less; perhaps in the range of $10/test or less.

Dose of Vitamin D.

McCullough *et al.* (2019)[11] studied patients in a psychiatric hospital. This included more than 4,700 patients, most of whom agreed to supplementation with either 5,000 or 10,000 IU/day. Some took larger doses ranging from 20,000 to 50,000 IU/day. They found that "*There have been*

no cases of vitamin D3 induced hypercalcemia or any adverse events attributable to vitamin D3 supplementation in any patient." Hypercalcemia is excess calcium in the blood that can result in bone pain, muscle weakness, stomach upset, nausea, vomiting and constipation. Controls (777 non-supplemented subjects) had mean calcidiol/25-OH-VitD3 levels of 27.1 nanograms/milliliter (ng/mL) (range 4.9 to 74.8 ng/mL). Supplemented subjects (418) had calcidiol/25-OH-VitD3 levels of 118.9 ng/mL (range 74.4 to 384.8 ng/mL). Mean serum calcium 0.95 mg/ml (no VitD3) vs 0.96 mg/mL (with VitD3), with ranges of 0.84 to 1.07 (no VitD3) vs 0.86 to 1.07 mg/mL (with VitD3). Thus, supplementation with VitD3, 5,000 to 50,000 IU/day for 12 to 29 days appeared to have been safe.[11] There have been other studies published with similar results and conclusions.

Historically, doses of 60,000 to 300,000 IU/d have been used for asthma, 150,000 to 600,000 IU/d for rheumatoid arthritis, and 100,000 to 150,000 IU/d for tuberculosis infections.[11]

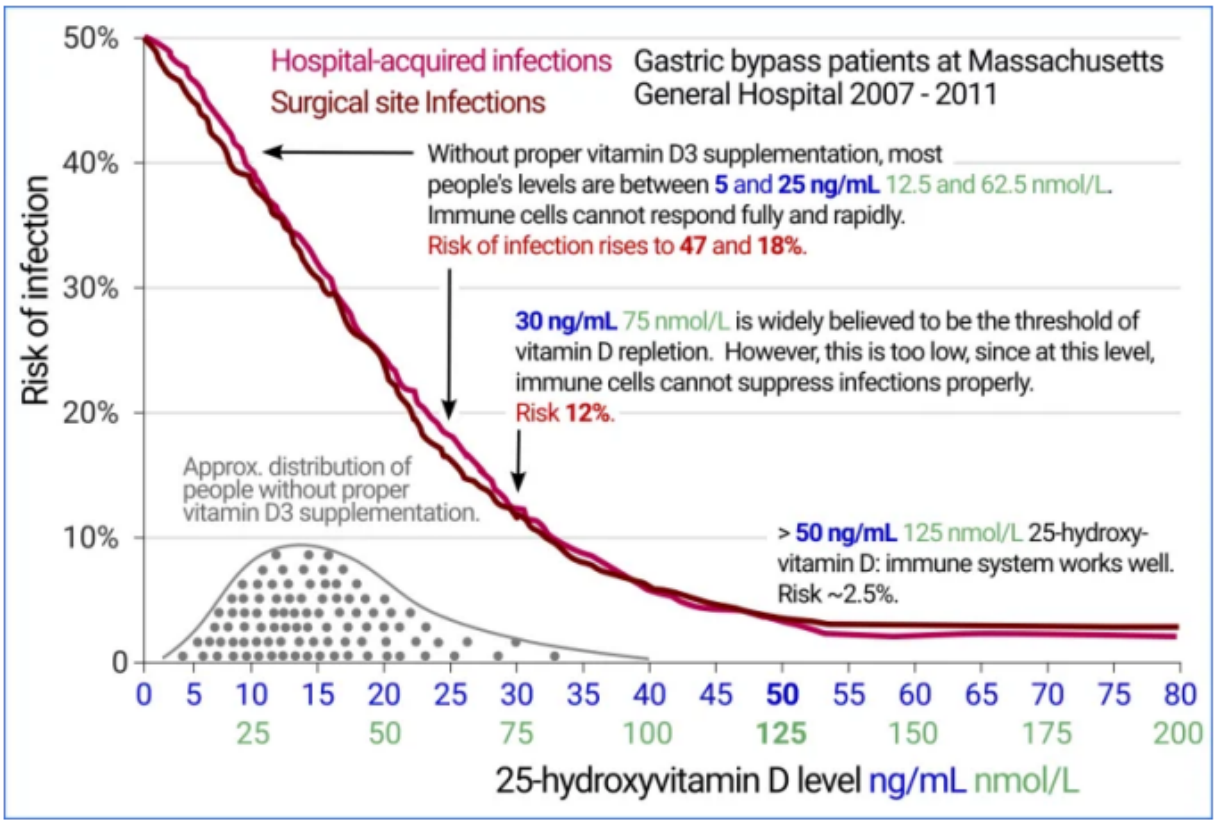
A comprehensive review by Vieth[12] in 2007 on the risk of daily dosing with VitD also concluded that 10,000 IU/day should be the safe tolerable upper intake level, and estimated that calcidiol/25OHD3 blood levels above 240 ng/mL were required to result in clinically significant hypercalcemia.

For context, the VitD made by human skin can be in the order of 20,000 IU in less than a day, as reported in a 2019 publication by Religi *et al*.[13] based on data from Switzerland, a country at similar latitude to Canada. These authors found that in summer and spring, with 22% of uncovered skin, 1,000 IU vitamin D doses are synthesized in 10-15 minutes of sun exposure for adults, or about 4,000-6,000 IU/h. A longer day in the sun is often said to result in a dose of vitamin D of 20,000 to 25,000 IU.

Appendix 1 comprises references that describe doses of VitD that have been suggested to address the various hypovitaminosis D conditions (low levels of VitD). The range is from 4,000 to 10,000 IU/day.

In summary, a daily dose of 4,000-6,000 IU should be safe for the population and fulfill much of the human health needs. This is above the 400-800 IU/d currently recommended by Health Canada.

Figure 2. Target serum level. Graph from Quraishi *et al*. (2014).[14]



Health care savings.

Considering the breadth of VitD actions and its necessity for health, hypovitaminosis D must be a substantial drain on Canadian healthcare. Grant *et al.* (2010)[15] have estimated the cost of VitD insufficiency for the country. Using both international and Canadian databases, these authors have estimated the cost of insufficient VitD attributed to cancer, cardiovascular disease, type 2 diabetes, multiple sclerosis, falls/fractures, influenza/pneumonia, septicemia and pregnancy outcomes. Total health spending in Canada was estimated to be $344 billion in 2023.[16] And the proportion of this due to VitD being 67 nmol/L instead of 100 nmol/L was conservatively estimated to be 6.9%; in other words, the annual savings due to creating VitD sufficiency would be about $23.7 billion.

But it would do more than just save money; it would significantly reduce the strain on healthcare facilities and personnel (doctors, nurses, pharmacists, technologists, *etc*.). However, the most

important advantage would be an improvement in the health of all Canadians especially those now without a family physician.

Implementation.

We appreciate that overcoming hypovitaminosis D in greater than 40 million people will be a challenge. But it does not have to be done immediately (but sooner is better), and we vaccinated over 30 million citizens in a few months during 2021. Moreover, such a project should be evaluated thoroughly, with the analysis of ample data collected during its implementation. We suggest that this should be considered as a research project conducted under the auspices of Canada's three federal research agencies, the Canadian Institutes of Health Research, the National Science and Engineering Research Council, and the Social Sciences and Humanities Research Council. This has the potential to attract experienced investigators, competent administrators and enthusiastic graduate students. Moreover, academic investigators are accustomed to conducting research work with limited amounts of funding. But this is putting the cart before the horse; let us first agree on supplementation and then decide on implementation.

Vitamin D toxicity.

VitD is fat-soluble raising a concern that like other similar substances, it could accumulate in the human body to induce a toxic reaction. Despite this possibility, the occurrence of adverse reactions among those taking VitD supplements has been remarkably rare. Perhaps this should have been anticipated because regular body exposure to direct sunlight can be tolerated; sunlight can create as much as 20,000 IU in half an hour. Nevertheless, several reports of VitD toxicity have been reported in the literature. The fact that case reports are worthy of publication suggests that the risk of VitD intoxication is rare but real.[17] As described by Alkundi *et al.* (2022)[17] in their case report, a middle-aged male had taken 15,000 IU daily for four months. He complained of recurrent vomiting, nausea, abdominal pain, leg cramps, tinnitus, dry mouth, increased thirst, diarrhoea, and weight loss. His blood tests revealed elevated serum calcium (albumin adjusted) (3.9 mmol/L; normal reference (ref): 2.2–2.6 mmol/L), acute kidney injury with serum creatinine (0.166 mmol/L; ref: 0.064–0.106 mmol/L), and urea of 13.4 mmol/L; ref: 2.5–7.8 mmol/L). His serum VitD was recorded as above 400 nmol/L. According to Jones (2008),[5] VitD (as cacifediol/25-

OH-VitD3) must rise above 750 nmol/L to produce toxicity and limiting it to 250 nmol/L should ensure a safety margin.

Holick (2015)[18] in an editorial entitled "*Vitamin D Is Not as Toxic as Was Once Thought: A Historical and an Up-to-Date Perspective*" stated "*Vitamin D intoxication associated with hypercalcemia, hyperphosphatemia, and suppressed parathyroid hormone level is typically seen in patients who are receiving massive doses of vitamin D in the range of 50,000 to 1 million IU/d for several months to years. Ekwaru et al.[16] recently reported on more than 17,000 healthy adult volunteers participating in a preventative health program and taking varying doses of vitamin D up to 20,000 IU/d. These patients did not demonstrate any toxicity, and the blood level of 25(OH)D in those taking even 20,000 IU/d was less than 100 ng/mL. For point of reference, a 25(OH)D level of 100 ng/mL is considered by the Institute of Medicine, the Endocrine Society, and many reference laboratories to be the upper limit of normal.*"

The number of cases of VitD toxicity as reported in VigiAccess (World Health Organization database of adverse drug reactions) has varied from a high of 1,136 cases in 2019 to a low of 781 cases in 2022. This compares favourably with acetaminophen (aka- paracetamol or Tylenol), which had 22,734 adverse effect cases reported in 2019 and 12,329 cases in 2022.

According to Holick (2022)[19] lifeguards typically have reported levels of calcidiol/25-OH-VitD3 of 100-125 ng/mL and there are no cases of VitD intoxication from sun exposure. VitD intoxication is defined as a 25-OH-VitD3 greater than 150 ng/mL (375 nmol/L) associated with hypercalcemia, hypercalciuria and often hyperphosphatemia. Similarly, Hathcock *et al.* (2007)[20] have concluded that the absence of toxicity in trials conducted in healthy adults indicates the VitD dose ≥0.25 mg or 10,000 IU/day can be considered a safe upper limit.

One means by which the body defends itself against VitD toxicity is through induction of the cytochrome P450 enzyme CYP24A1 by calcitriol/1,25$(OH)_2$VitD3. This prevents the accumulation of toxic levels of calcitriol/1,25$(OH)_2$VitD3 and calcidiol/25-OH-VitD3 by catalyzing the formation of an inactive metabolite, calcitroic acid (Figure 1).

VitD Toxicity in Pets.

Users may know that VitD in large doses has been developed as an alternative to warfarin as a varmint (rat) poison. Nevertheless, pets such as dogs and cats would have to ingest much more VitD than the doses used by humans to become intoxicated. The main risk would be ingestion of VitD containing rodenticide baits.[21] The oral lethal dose for 50% death (LD_{50}) of cholecalciferol in rats is 43.6 mg/kg (1,744,000 IU/kg).

Vitamin K2 to The Rescue?

We now know that vitamin K2 has many important beneficial effects, one of which is to ensure proper distribution of calcium into bones and away from soft tissues, especially blood vessels. This would address some of the effects of hypercalcemia resulting from excess VitD. As this document is focused on VitD, we refer the reader to a useful recent review by Kozioł-Kozakowska and Maresz (2022)[22] on vitamin K2 in children's health and diseases.

A first principle in the nutrition field is that proper or optimal nutrition is the result of all of the individual components working and acting together. Thus, VitD works best when combined with optimal supplies of several other nutrients such as Vit K2. We do not have to wait for expensive, controlled trials to act in the best interests of our citizens. There is enough evidence to justify VitD supplementation. Individual citizens, working with their doctors and other healthcare professionals can take existing information on VitD *per se* and combine it with knowledge of vitamin K2 to further optimize their health maintenance. While it is known that magnesium is also important in the context of VitD sufficiency, this subject is reserved for another article. These refinements can occur in further implementation of a national strategy on nutritional optimization for health maintenance.

Confounding factors.

A major difference between studies on VitD and other treatments, such as novel drugs, is the impossibility of having a comparative control population that has no VitD in their bodies. Everyone has some level of VitD in their bodies.

Vitamin D Testing.

The rationale presented above is intended to ensure that VitD is used effectively and safely. A key factor in implementing VitD sufficiency for all citizens would be the opportunity to access VitD testing, which is not covered by all provincial health plans. Nevertheless, such testing would be a health investment that would pay for itself many times over. Moreover, market forces almost certainly could drive the introduction of cheaper and more convenient tests to measure VitD levels.

Appendix 1- Benefits of Vitamin D Supplementation.

The literature on VitD is massive and cannot be covered comprehensively in this document. Nonetheless it is possible to cite sufficient examples of studies and reviews, which illustrate the potential benefits of full VitD sufficiency of the Canadian population.

- **All-cause mortality**.

  In a study by Dai *et al.* (2021),[9] the authors noted, "*Among 37,079 patients with CVD at baseline, 57.5% were subjected to vitamin D deficiency (i.e., 25[OH]D <50 nmol/L). During a median follow-up of 11.7 years, 6,319 total deaths occurred, including 2,161 deaths from CVD, 2,230 deaths from cancer, 623 deaths from respiratory disease, and 1,305 other-cause deaths. We observed non-linear inverse associations for all-cause, cancer, respiratory disease, and other-cause mortality (P-non-linearity <0.01) and approximately linear inverse associations for CVD mortality (P-non-linearity = 0.074). Among CVD patients with vitamin D deficiency, per 10 nmol/L increment in serum 25(OH)D concentrations was associated with an 12% reduced risk for all-cause mortality and 9% reduced risk for CVD mortality*."

- **Multiple sclerosis (MS).**

  With respect to VitD application, this is a good news story as MS specialists recommend VitD supplementation and Quebec still provides VitD testing within the public health plan.

  MS, a disease affecting the brain/spinal cord to produce significant disability, features an incidence that increases with increasing latitudes therefor populations (like Canadians) further from the equator have more MS cases.[23] This led to the concept that insufficient VitD is a factor in the development of MS. Also, genetic studies in MS have unveiled abnormalities of

VitD metabolism linked to an increased risk of MS.[24] For information regarding the mechanism of VitD effects in MS, see immune effects below. Several studies have addressed the potential utility of VitD for the prophylaxis and treatment of MS.[25] Nevertheless, robust clinical trials unequivocally revealing the benefit of VitD in this disease are still lacking (mainly due to the high cost). On the basis of current evidence, MS specialists and the MS Society of Canada recommend supplementation with vitamin D[26, 27] set for the general public by the Institute of Medicine and also recommended by Health Canada - "*adults should achieve and maintain a normal vitamin D status with monitoring by physicians (serum 25-hydroxyvitamin D (25OHD) = 50–125 nmol/L, requiring intake of 600–4000 IU vitamin D/day).*" Also, "*Because low serum 25OHD during childhood and adolescence is associated with increased MS risk, pregnant women, newborn infants, and all youth should follow DRI (Dietary Reference Intake) recommendations for vitamin D intake, including age specific recommendations for vitamin D supplements*."

Age group	**Recommended daily intake**	**Maximum daily intake**
Infants 0-6 month-olds	400 IU	1000 IU
Infants 7-12 month-olds	400 IU	1500 IU
Children 1-3 year-olds	600 IU	2500 IU
Children 4-8 year-olds	600 IU	3000 IU
Children and adults 9-70 year-olds	600 IU	4000 IU
Adults >70 year-olds	800 IU	4000 IU
Pregnant and breastfeeding women	600 IU	4000 IU

Table reproduced from the document "MS Society of Canada Recommendations on Vitamin D in MS."[27] These guidelines also state that "*people living with MS should target serum 25-hydroxyvitamin D of 50–125 nmol/L*."

- **Cancers.**

  Two factors work against researchers attempting to demonstrate that VitD decreases the incidence of cancers; these are the long period between exposure to a carcinogen and diagnosis of cancer as well as variable blood levels of VitD especially in lower latitude regions where greater exposure to sunlight is possible. The duration effect is seen in Figure 2 from a study by Chandler *et al.* (2020),[28,] wherein the cumulative incidence of metastatic and fatal cancers of any type show no effect of VitD supplementation for two years and then show greater protective effects of VitD in subsequent years.

Wu *et al*. (202*3)*[29] in their recent prospective study of data from the UK Biobank comprising 97,621 participants revealed that individuals with metabolic syndrome but with sufficient VitD status (> 75 nmol/L) had a 25% and 35% lower risk for 16 different cancers and all-cause mortality, respectively, over 12.7 years as compared to those with VitD deficiency (< 25 nmol/L).

Song *et al.* (2018)[30] conducted a meta-analysis on the effects of VitD on mortality in patients with prostate cancer. Seven eligible cohort studies with 7,808 participants were included. Higher VitD levels correlated with decreased mortality from prostate cancer as each 20 nmol/L increment in calcidiol/25-OH-VitD3 level was associated with a 9% lower risk of all-cause mortality and prostate cancer-specific mortality.

- **Cardiovascular diseases (CVD).**

  Although there are many reviews indicating that adequate VitD is associated with reduced cardiovascular diseases, there is still much research needed to define the extent of the clinical response and the exact mechanisms involved. Nevertheless, the extant evidence is arguably sufficient to recommend VitD supplementation as part of the strategy to prevent and treat many cardiovascular diseases. In other words, we suggest that VitD supplementation applied to the VitD insufficient population is justified now, and that further delay is tantamount to causing harm.

  The risk of cardiovascular disease with respect to VitD levels was analyzed by Zhou *et al.* (2022)[31] with data from the UK Biobank with 44,519 CVD cases and 251,269 controls. They estimated the potential reduction in CVD incidence attributable to a correction of low VitD status. There was an L-shaped association between genetically predicted serum 25-OH-VitD3 and CVD risk (P non-linear = 0.007), where CVD risk initially decreased steeply with increasing concentrations and levelled off at around 50 nmol/L. A similar association was seen for systolic (P non-linear = 0.03) and diastolic (P non-linear = 0.07) blood pressure. Correction of serum 25-OH-VitD3 level below 50 nmol/L was predicted to result in a 4.4% reduction in CVD incidence (95% confidence interval: 1.8– 7.3%). They concluded that vitamin D deficiency can increase the risk of CVD and that CVD could be reduced by population-wide correction of low VitD status.

With respect to hypertension, there are strong data indicating that VitD deficiency likely plays an important role in the development of this condition. Moreover, a plausible mechanism has been revealed using laboratory animal studies. The Ludwigshafen Risk and Cardiovascular Health (LURIC) study[32] showed that $1,25(OH)_2VitD_3$ was inversely associated with plasma renin and angiotensin II levels. VitD analogues suppress plasma renin activity in patients. The mechanism as elucidated in animals is that $1,25(OH)_2VitD_3$ inhibits renin gene transcription through the cyclic-AMP signalling pathway.[33]

- **Lung diseases. Bacterial and viral pneumonia.**

  A systematic review and meta-analysis by Martineau *et al.* (2017)[34] comprising 11,321 participants from 25 eligible randomized placebo-controlled trials having individual participant data, provided high quality evidence to support that VitD supplementation is a safe intervention to prevent the risk of acute respiratory tract infections. In another review, Borshe *et al.* (2021)[35] addressed the question of whether poor VitD status is caused by respiratory illness, or whether VitD deficiency predisposes an individual to SARS-CoV-2 infection and severe COVID-19 disease. Accordingly, they included studies in which patients' pre-infection VitD levels were documented and also some in which VitD levels up to the day after hospitalization were recorded. Their analysis revealed a significant negative correlation between VitD pre-infection concentrations and mortality. Extrapolation of the regression line to the x-axis implied that the risk of death could virtually disappear at 125 nmol/L; that represents a therapeutic target for circulating calcifediol/25-OH-VitD_3 needed for optimal immune function. Indeed, recent studies have demonstrated that the VitD status of hospitalized COVID-19 patients was inversely associated with chest X-ray severity scores and various biomarkers of inflammation and clotting activity, including tumour necrosis factor-alpha, interleukin-6, C-reactive protein, ferritin and D-dimer levels.

- **Brain diseases (Alzheimer & Parkinson).**

  In a recent review by Pinzon *et al*. (2023)[36] a total of 6 studies were included, involving 10,884 participants. The analysis showed that patients with VitD deficiency (< 25 ng/mL) had a higher risk of Alzheimer disease compared to patients with adequate VitD supply (≥ 25 ng/mL) (HR: 1.59, 95% CI: 1.09, 2.33, I2=77%).

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A subsequent study by Ghahremani *et al.* (2023)[37] reported that VitD exposure was associated with 40% lower dementia incidence versus no added exposure. The University of Calgary team "*prospectively explored associations between vitamin D supplementation and incident dementia in 12,388 dementia-free persons*" used data from the National Alzheimer's Coordinating Center database. There were 12,388 participants in the VitD supplemented group, who had been exposed to some form of VitD supplements, and 4,637 controls who had not taken any VitD supplements. From all subjects, 2,696 progressed to dementia in 10 years; of these 2,017 (74.8%) had no VitD supplements and 679 (25.2%) were exposed to VitD supplements. After several adjustments, VitD exposure was associated with a 40% lower incidence of dementia (HR=0.60, 95% CI: 0.55–0.65, p<0.001). Remarkably, this benefit of VitD supplementation was observed despite the lack of any attempt to optimize the dose of VitD consumed. It is tempting to suggest that VitD supplementation could lower the odds of dementia by more than 40%.

Considering Canada's aging population and increasing diagnoses of dementia, widespread VitD supplementation would appear to be a logical beneficial public health measure.

- **Type 2 diabetes (DM2).**
  A review by Pittas *et al.* (2013)[38] of three randomized trials revealed that in adults with prediabetes, VitD was effective in decreasing the risk for diabetes. Among participants assigned to the VitD group, who maintained an intra-trial mean serum 25-OH-VitD3 level of at least 125 nmol/L (≥50 ng/mL) compared with 50 to 74 nmol/L (20 to 29 ng/mL) during follow-up, cholecalciferol/VitD3 reduced the risk for diabetes by 76% (hazard ratio, 0.24 [CI, 0.16 to 0.36]), with a 3-year absolute risk reduction of 18.1% (CI, 11.7% to 24.6%).

- **Inflammatory bowel disease (Crohn's disease, ulcerative colitis).**
  While there is strong circumstantial evidence for a role of vitamin D in intestinal health, VitD has not yet been shown to be predictive of preventing inflammatory bowel diseases or curing them.

- **Immune system.**
  Leukocytes such as activated B and T lymphocytes, macrophages, dendritic cells, neutrophils, mast cells and eosinophils express VDR,[39, 40, 41] as well as the enzymes CYP27B1 and CYP24A1, which enable leukocytes to regulate intracellular bioactive VitD levels. Collectively, these

support an important immunomodulatory role for VitD. In support of this, VitD deficiency has been found to be a risk factor for microbial infection, especially intracellular bacterial and viral diseases, immune disorders including autoimmune diseases and allergies[39] and cancers.[42]

Numerous genes involved in immunoregulation are directly responsive to VDR after it has bound to VDR response elements within gene promoter or enhancer regions;[43] examples include genes regulating antigen presentation (MHC genes), cell trafficking (chemokines and chemotactic agents), cell activation (cytokines), pathogen recognition (pattern-recognition receptors) and antimicrobial peptides.[44] However, VitD also has non-genomic mechanisms of regulating immediate leukocyte function that include binding to an alternate VDR (PDIA3) found within the cell membrane, cytoplasm, mitochondria and nucleus.[45]

VitD's immunomodulatory properties are broadly attributed to regulating leukocyte differentiation, maturation, responsiveness to cytokines and chemokines, and cell metabolism.[46] More specifically, VitD regulates cells of the innate immune system by supporting production of neutrophil antimicrobial peptides, differentiation of inflammatory M1 macrophages to tissue repairing M2 macrophages, and arresting dendritic cell maturation so that they remain capable of producing immunological tolerance. In terms of the acquired immune system, VitD supports the terminal differentiation of T cells to regulatory T cells instead of inflammatory Th1 and Th17 cells, and apoptosis (programmed cell death) of activated B cells. It also inhibits B cell differentiation into immunoglobulin-producing plasma cells and their immunoglobulin class switching.

Schwalfenberg (2010)[47] has suggested that the several infectious conditions such as tuberculosis, chest infections, influenza, urinary tract infections, eye infections, wound infections, and wound healing may benefit from adequate VitD.

- **Pregnancy and vitamin D.**

  The concepts of Developmental Origins of Health and Disease (DOHaD) describe how maternal nutrition during pregnancy affects the health of offspring during later life, including adulthood. Exactly how VitD might play a role in DOHaD is yet to be elucidated. Nevertheless, Amegah *et al.* (2017)[48] have found that VitD insufficiency was associated with risk of preterm birth. In their report entitled, "*Vitamin D: Before, during and after Pregnancy: Effect on Neonates and*

Children", Mansur *et al.* (2022)[49] described evidence that VitD is helpful in reducing the risk to mothers of pre-eclampsia, gestational diabetes, caesarean section and preterm delivery as well as reducing the risk to their offspring of low birth weight, low bone mass and possibly also bronchiolitis, asthma, type 1 diabetes, multiple sclerosis and autism.

Supplementation of mothers with VitD during pregnancy affects the microbial population within their offspring,[50] which may have positive implications for asthma and respiratory infections.

VitD deficiency during gestation results in increased risk of obesity in their offspring.[51]

- **Mental health**.

  Although studies on the relationship between VitD and mental health are sparse compared with those on physical health, most such reports indicate that adequate VitD is necessary for good mental health. At the earliest stage of life, optimal maternal VitD appears to be essential for the good mental health of offspring.[52] Thus, low maternal VitD dosage during gestation has been related to a significantly greater risk to develop schizophrenia and other severe mental illnesses in later life.

  During the subsequent stage of life, childhood, VitD is similarly necessary for good mental health. Glabska *et al.* (2021)[53] in their review "*The Influence of Vitamin D Intake and Status on Mental Health in Children: A Systematic Review*," addressed "*behavior problems, violence behaviors, anxiety, depressive symptoms/depression, aggressive disorder, psychotic features, bipolar disorder, obsessive compulsive disorder, suicidal incident, as well as general patterns, as follows: mental health, level of distress, quality of life, well-being, mood, sleep patterns*." Included were both interventional and observational studies. With few exceptions, the data indicated a positive relationship between supplementary treatment with VitD or positive relationship between VitD levels and mental health indicators. The doses of VitD used in such studies was generally in a range that would be considered moderate compared to the higher doses being used in contemporary physical medicine, and the VitD blood level criteria were also moderate.

Studies of adults appear to differ from those in children as described by Guzak *et al.* (2021)[54] in their review of the literature, "*Association between Vitamin D Supplementation and Mental Health in Healthy Adults: A Systematic Review*." These authors found that "*results of the majority of studies did not confirm a positive influence of vitamin D supplementation*."[54] The authors also commented on the difficulty encountered when evaluating the effect of a treatment such as VitD as there is always a background level of VitD. This varies significantly based on cultural variables such diet and location. At this point, we cannot suggest a standard VitD intake or blood level for the maintenance of optimal mental health in adults.

- **Oral Health.**

  VitD deficiency has a significant effect on oral health. This should not be surprising considering the role that VitD plays in the mineralization of teeth and their supporting alveolar bone. In addition, this vitamin assists in maintaining the integrity of the gums and, via saliva, assists in modulating immunologic and antimicrobial activities.

  VitD deficiency results in a defective dentition in which the enamel is thinner or less mineralized than normal. The dentine or inner hard layer is less mineralized. The pulp chamber containing blood vessels and nerve fibres is larger than normal and tooth roots are shorter than usual.[55] These physical defects are associated with teeth that are prone to fracture, malocclusion, and periodontal disease.[55] While current evidence indicates an association between VitD deficiency and increased dental decay in children and adults, the causes are unclear.[56]

  Faulty development of the enamel can occur *in utero*. Classically this appears as a band of poorly formed or pitted enamel on the deciduous teeth corresponding to the period at which the mother had a VitD deficiency. Supplementation with VitD during pregnancy has been associated with a 50% reduction in enamel defects of the newborn.[57]

  Periodontitis is a polymicrobial chronic inflammatory disease that destroys the soft and hard tissues which support the tooth in its socket resulting in increased tooth mobility and possible tooth loss. Although VitD deficiency might affect tooth mineralization and that of the supporting alveolar bone thus promoting periodontitis, the relationship between Vitamin D

levels and periodontitis remains questionable.[56] Several studies have demonstrated an association between decreased levels of VitD and the clinical signs of periodontitis, such as inflamed, bleeding gums.[58, 59]

There are reports that pregnant women with lower levels of serum VitD have moderate to severe periodontitis compared to women with good periodontal health.[60] The non-surgical treatment of periodontitis has benefitted from VitD and calcium supplementation, again supporting a relationship between adequate levels of VitD and periodontal integrity.[61] Orthodontic treatment depends on alveolar bone resorption in front of the moving tooth and bone formation behind it. Animal studies have demonstrated that by interfering with bone metabolism, VitD deficiency inhibits tooth movement and induces treatment complications. Further research might indicate the usefulness of VitD supplementation in minimizing the complications and reducing the duration of orthodontic therapy.[62] VitD deficiency has been associated with an increased risk of oral, esophageal, and pharyngeal cancers.[63] Foci of osteonecrosis (dead bone) within the mandible or maxilla occasionally occur following radiation therapy for oral and pharyngeal malignancies and as a side effect of bisphosphonate (Fosamax) therapy in controlling osteoporosis. Whether VitD deficiency is a risk factor for the development of osteonecrosis or if VitD supplementation will reduce its occurrence, remain undecided.[64]

VitD deficiency reduces the flow rate of saliva and its ability to neutralize the acidogenic bacteria responsible for dental decay.[65] These factors, in combination with a loss of salivary immune regulation and antimicrobial properties, are other reasons which explain an association between VitD deficiency and increased susceptibility to dental decay and the promotion of oral pathogens.[66]

Of the total estimated Canadian health expenditure for 2022 of $344 billion,[67] 5% or $1.5 billion can be attributed to oral diseases, most commonly tooth decay and periodontitis. The association between these conditions and VitD deficiency justifies maintaining optimal levels of VitD.

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Other resources.

MS Society. https://mscanada.ca/vitamin-d-multiple-sclerosis
Vitamin D Society. https://www.vitamindsociety.org
https://www.canadiansfortruth.ca/about-us
https://dgreatbiologyreset.com/ANDERSON-GRIMES-Vitamin-D3-and-the-Great-Biology-Reset-D3DE.pdf

Vitamin D testing. Test kits sold by ImmunoCeutica (https://immunoceutica.ca), Guelph, ON.