

The Vitamin D Gamble

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Studies have shown that most Canadians are deficient in Vitamin D₃. In addition to its role in systemic calcium regulation, Vitamin D₃ is also proposed to be integral to the suppression of cancer, as well as to the regulation of certain immune and endocrine components. Many experts are seriously concerned that Health Canada's current Vitamin D₃ dosage recommendations are inadequate to facilitate these mechanisms. A bitter debate on dosage has ensued—largely between researchers and regulatory bodies such as Health Canada and the US Institute of Medicine—leaving health practitioners caught in the middle with contradictory directives and information.

Vitamin D is the colloquial term for Vitamin D₃, a secosteroid prohormone that is naturally produced in certain layers of the skin.¹ It is endogenously synthesized from a naturally occurring precursor called 7-dehydrocholesterol (7-DHC), which undergoes further conversion upon continued exposure of the skin to moderately intense light in the UV-B range.²

In addition to its well-known role in maintaining the mineralization of bone, research over the past few decades has unveiled multiple potential non-classic actions of Vitamin D₃.³ Apart from causing severe bone disorders, deficiencies in Vitamin D₃ are also thought to contribute to the development of many life-threatening cancers, the emergence of a wide variety of autoimmune disorders, increased bacterial susceptibility, and the appearance of a number of diseases resulting from hormone dysregulation (such as diabetes and osteomalacia).³

Unfortunately, most Canadians live with insufficient levels of Vitamin D₃ in their bodies.⁴ Even in the southernmost extremities of Canada, the latitude and quality of sun exposure during early fall to mid-spring does not provide sufficiently intense exposure of the human skin to UV-B radiation.¹ This results in minimal endogenous Vitamin D₃ production during these months. The use of sunscreens, while important in reducing the risk of melanoma, inhibits the production of Vitamin D₃ during the summer months and further compounds this deficiency.²

In March 2010, Statistics Canada estimated that 1.1 million Canadians (approx. 4% of the Canadian population) had a Vitamin D₃ deficiency so extreme that they were at risk of acquiring osteoporosis or osteomalacia if they were adults, and rickets if they were children.⁵ The study also found that 10% of Canadians had levels that are inadequate for maintaining bone health, and that 77% of the population did not have appropriate serum levels by Health Canada's standards.⁶

Over the past few decades, hundreds of clinical studies have pro-

vided evidence that dietary supplementation is an effective way to compensate for inadequate endogenous Vitamin D₃ production. As such, there is a unanimous agreement in the Canadian health science community that the nationwide deficiency can only be effectively overcome by ensuring Canadians include adequate Vitamin D₃ supplements in their diet.⁷

At this point, however, the unanimity ends. Largely outside public view, a fierce debate has emerged over the definition of an “adequate” supplemental dose. On November 30, 2010, Health Canada and the US Institute of Medicine (IOM) co-released the controversial publication, *Dietary Reference Intakes (DRIs) for Vitamin D and Calcium*.⁷ In this report, Health Canada and IOM took a conservative stance, recommending 600 IU of Vitamin D₃ per day for all persons of 9-70 years of age, 400 IU for young children and infants, and 800 IU for adults over 70 years. It also set the Tolerable Upper Intake Level at 4,000 IU for those older than 9 years.⁷ These dosage recommendations differ only slightly from those of the Canadian Cancer Institute, which states that 1,000 IU per day is adequate for the majority of the adolescent and adult population.⁸ By contrast, a significant number of researchers in the field recommend substantially higher daily dosages of between 2,000-4,000 IU for those above 9 years. Many of them also believe that the upper cap could be safely set to 10,000 IU before any toxic overdose effects are seen.⁹⁻¹¹ Health practitioners—those who are tasked with providing advice to their patients—are caught in the middle, working with contradictory directives and information.

NON-CLASSIC ACTIONS OF VITAMIN D₃

Why have so many researchers taken a seemingly radical stance on Vitamin D₃ dosage recommendations? Predominantly, many are worried that a number of the non-classic actions of the vitamin—including its purported role in suppressing carcinogenesis, maintaining the immune system, and regulating critical hormone levels—are not sufficiently facilitated when taken at low-dosages.

Vitamin D₃ is thought to be involved in the suppression of various cancers, including those of endothelial tissue and bone, and possibly breast, colorectal, and pancreatic cancers.³ The influence of Vitamin D₃ on the latter three cancers is still debated and merits further research, however, there are conflicting data from published epidemiological, geographical, laboratory, and clinical studies.¹² Regardless, it is generally agreed upon that adequate levels of Vitamin D₃ can assist in the successful differentiation of endothelial and bone cells and can suppress uncontrolled, rapid cell proliferation.¹³

Once produced or ingested, Vitamin D₃ is initially inactive. It is rapidly hydroxylated in the liver to form the hormone 25(OH)D₃, and subsequently enters the circulation. In the kidneys, it is hydroxylated on-demand once more, forming the active hormone 1,25(OH)₂D₃.¹ The latter hormone binds with Vitamin D₃ receptors (VDRs) that are located in a range of tissues.³

Many of the early cancer studies in the 1990s focused on the protein-modulating nuclear activity of activated VDRs and the Retinoid X Receptor (RXR) heterodimer, as well as Vitamin D₃-DNA intercalation.¹³ Given recent advancements in gene regulation research and analytical technologies, however, studies have also discovered VDR-independent activity of Vitamin D₃.¹⁴ They have pinpointed a variety of pro-oncogenic and anti-oncogenic transcription factors that are actively regulated by non-hydroxylated Vitamin D₃.¹⁴ Many of these transcription factors are expressed only in specific cell types, and hence the mechanisms of cancer-suppression are thought to vary widely between different tissues.³

A major study recently conducted by the University of Maryland postulated that the DNA-binding affinity of the RUNX2 transcription factor is increased by non-hydroxylated Vitamin D₃ in endothelial, bone, and breast cells.¹⁶ In osteoblast cells in the bone, increased RUNX2 DNA-binding affinity amplifies the expression of cancer-suppressing proteins that stimulate immature osteoblastic differentiation and inhibit rapid osteoblastic proliferation.^{13,16} Within cancerous breast cells, it also ensures that such cells do not stimulate the metastatic cancerous development of osteoblasts—thus helping to prevent the spread of cancer from breast to bone.¹⁶

Meta-analyses of clinical and community studies in the breast cancer field have found that Vitamin D₃ supplement doses must be in the range of 2,000 IU and 3,000 IU per day to begin to see any reduced risks of cancer.¹⁷ In other areas, doses exceeding 1,000 IU are found to be necessary.⁹

Vitamin D₃ also plays a crucial role in regulating both the innate and adaptive components of the internal immune system. Without appropriate levels of the compound, animals are found to have an increased susceptibility to bacterial infection, as well as to autoimmune disorders such as multiple sclerosis, rheumatoid arthritis, Type I diabetes mellitus, inflammatory bowel disease, certain forms of lupus, and pre-natal islet cell autoimmunity.¹⁸

The innate immune system is comprised of non-selective defense mechanisms that destroy pathogens. Some of these mechanisms involve the use of proteins that damage the structural integrity of bacterial cells.¹⁸ Vitamin D₃ acts as an intermediate signaling molecule in the production of certain bactericidal peptides, such as cathelicidin.³ These peptides coalesce within phagosomes and severely damage the cell membranes of ingested bacterial cells.¹⁸ When toll-like receptors (TLRs) on macrophages are activated, 1- α -hydroxylase (the enzyme catalyzing the hydroxylation of Vitamin D₃) and VDRs are immediately produced by the macrophage.^{3,18} Circulating 25(OH)D₃ in the blood is converted to 1,25(OH)₂D₃.^{3,18} This subsequently binds with VDR, causing the formation of a VDR-RXR heterodimer complex—allowing for transcription of cathelicidin.¹⁸ Deficiency in Vitamin D₃ is thus believed to handicap our ability to fight off bacterial infections, as it prevents the sufficient production of bactericidal proteins.¹⁸

The adaptive immune system, on the other hand, employs antigen-specific targeting that allows for “learned” elimination of pathogens by specialized cells.³ Vitamin D₃ is thought to be involved in specific mechanisms that suppress the autoimmune functions of this system.¹⁸ Under certain circumstances, such as an abnormally low level of immature dendritic cells (DCs) and high levels of inflammatory cytokine production by monocytes, the body begins to produce antibodies against its self-antigens.¹⁸ One of the roles of immature DCs is to present self-antigens to T-cells in a way that facilitates the buildup and maintenance of immune system tolerance to host cells. Too low a level of immature DCs can result in a low tolerance to the body’s own cells, leading to excessive autoimmune responses.¹⁸ By various complex mechanisms involving the differentiation of T- and B-cells, Vitamin D₃ inhibits DC differentiation and maturation, and thus preserves adequate levels

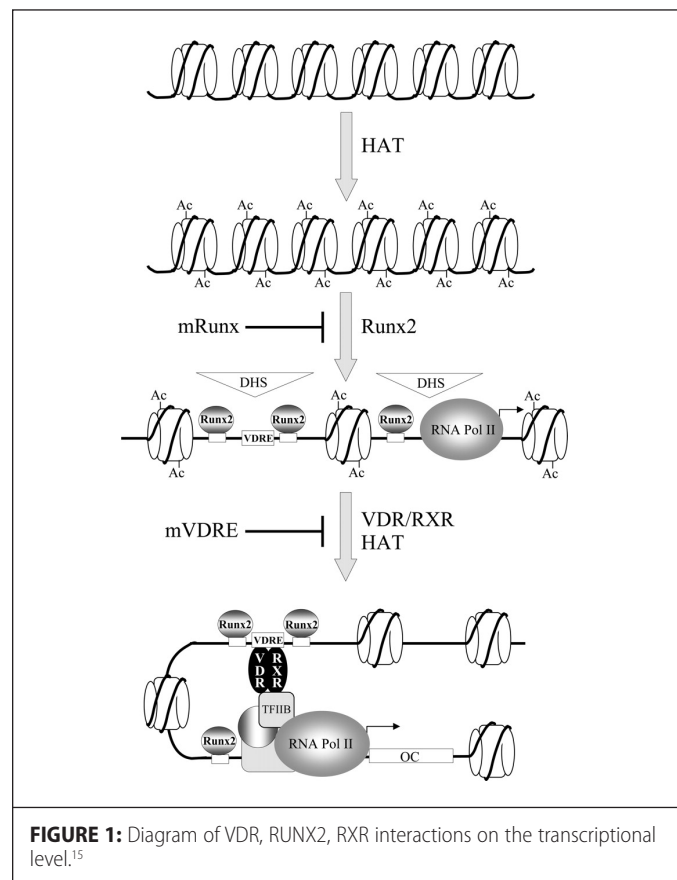
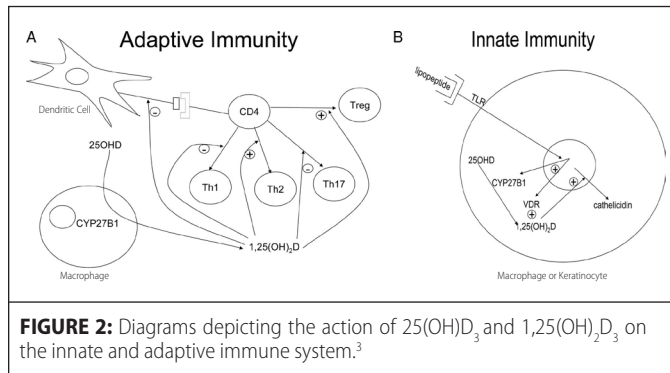


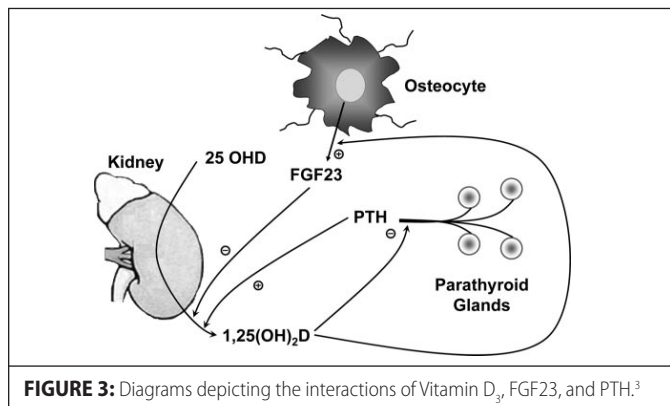
FIGURE 1: Diagram of VDR, RUNX2, RXR interactions on the transcriptional level.¹⁵

of the immature DC phenotype needed in order to suppress the development of autoimmune disorders.¹⁸ Vitamin D₃ also inhibits the production of inflammatory cytokines by monocytes and increases the production of anti-inflammatory cytokines, so that when autoimmune responses do occur, widespread inflammatory damage does not ensue.^{3,13,18}



Similar to the results of many clinical trials, Vitamin D₃ supplementation dosages used in studies testing MS- or other autoimmune-afflicted patients, only seem to produce positive results when exceeding levels of 4,000 IU per day.¹⁹ This is far above Health Canada's recommended dosage.

Finally, Vitamin D₃ also plays a critical role in hormonal regulation. Three major classes of hormones are regulated by Vitamin D₃ including Parathyroid hormone (PTH), Fibroblast Growth Factor 23 (FGF23), and insulin.³ The regulatory action of Vitamin D₃ on the first two hormones forms a negative feedback loop that modulates blood serum levels of 1,25(OH)₂D₃.³ This is accomplished by hormonal control over the transcription of 1- α -hydroxylase in the kidney. PTH upregulates this transcription and stimulates the hydroxylation of 25(OH)D₃ in the kidney to 1,25(OH)₂D₃. In contrast, FGF23 downregulates transcription of 1- α -hydroxylase, and inhibits further 1,25(OH)₂D₃ production. By interacting with VDRs, 1,25(OH)₂D₃ inhibits the further secretion of PTH and stimulates the production of FGF23.³ Together, the concentrations of 1,25(OH)₂D₃, PTH and FGF23 maintain serum 1,25(OH)₂D₃ levels at a constant and adequate level.³ When imbalances in these hormones occur, as caused by inadequate intake levels of Vitamin D₃, other conditions can develop, such as osteomalacia (in the case of FGF23).^{3,12}



Insulin, unlike PTH and FGF23, has a less-obvious connection with Vitamin D₃. Although the mechanism is not fully understood, it is thought that 1,25(OH)₂D₃ stimulates insulin secretion, largely through the interaction of VDRs with calbindin-D_{28K}.³ The latter, when fully activated, can also help to prevent the cytokine-mediated destruction of β -cells. Hence, Vitamin D₃ deficiency can lead to insulin dysregulation as well as an increased risk for Type I diabetes mellitus.³

THE DOSAGE DEBATE

The putative non-classic actions of Vitamin D₃ are considerable and diverse. Dosage plays a significant role in determining the effectiveness of Vitamin D₃ supplementation in driving these mechanisms.

Health Canada's previously mentioned report was published following a joint Canadian and US evaluation of existing research surrounding the disputed non-classic actions and their requisite dosages of Vitamin D₃.⁷ Surprisingly, the report concluded that the potential anti-cancer and auto-immune benefits of increased Vitamin D₃ intake have not yet been proven, nor the potential overdose risks, including kidney and other internal organ calcification, not yet accounted for.⁷ It even went so far as to declare that "there is no additional health benefit associated with Vitamin D intakes above the level of the new Recommended Dietary Allowance".⁷

Since the release of the report, many in the field have criticized its method of meta-analysis, describing it as overly-cautious and hyper-stringent.^{20,21} Many health practitioners had hoped for better guidance and expected a recommendation of at least 1,000 IU per day for any age category, the level thought to constitute the absolute minimum dose needed for any significant overall benefit.^{4,11,21} Perhaps Health Canada's stance is a consequence of the overblown Vitamin E-cardiovascular research throughout the 1990s, after which few claims were found to be entirely valid.²²

A recently-released American meta-analysis study seems to agree with Health Canada's position. The United States Preventive Services Task Force report states that a number of the clinical cancer-prevention studies lacked properly-controlled external variables such as family health history, while the statistical methods of others were not appropriate.^{23,24} They concluded that many of the proposed cancer-suppressing effects of Vitamin D₃ were not yet sufficiently evidenced. However, the report also judged that further research and re-evaluation are required to establish proper Vitamin D₃ dosage recommendations.^{23,24}

As the hype surrounding Vitamin D eventually diminishes and studies are performed that examine the validity of previous experiments and conclusions, we may see that the accepted scope of the vitamin's non-classic actions will recede. However, even if only a handful of these non-classic actions are proven, the potential therapeutic effects of vitamin D will still bolster general public health. ■

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