REVIEW ARTICLES

Vitamin D deficiency and its health implications: a review of the Canadian context

Kibur Hunie Tesfa[1]* and [2]Mulu Geletu[2]
[1]Department of Biochemistry, College of Medicine and Health Science, University of Gondar, Ethiopia
[2]Department of Chemical & Physical Sciences, University of Toronto Mississauga, Canada (mulu.geletu@utoronto.ca)

Corresponding Author: E-mail: kiburtesfa@gmail.com

ABSTRACT
The major cause of vitamin D deficiency is the lack of proper and ample exposure to sunlight. Only certain foods naturally contain vitamin D, and foods fortified with vitamin D are often insufficient to satisfy vitamin D requirements. Advertently or inadvertently, people avoid taking adequate sunlight, which is essential to attain the required level. Given the colossal ramifications of vitamin D deficiency, people must optimize their daily intakes to protect themselves from diseases resulting from vitamin D shortage. Vitamin D is critically significant for the absorption of dietary calcium and phosphate in circulation; it enables bone mineralisation by providing pertinent minerals to bone-forming and maintaining sites. The need for vitamin D must be prevented from occurring to enjoy a healthy life. It is also important that social institutions play a crucial role in custodianship by providing education, nutritional guidelines, and adequately monitoring the appropriateness of the preparation of vitamin D supplements. In this article, we attempt to address various health benefits that vitamin D brings and the dramatic health consequences on children and adults alike when there is vitamin D deficiency.

Keywords: *Vitamin D, Calcitriol, Vitamin D Deficiency, Cancer*

INTRODUCTION

Vitamin D, as the oldest hormone can be traced back to time immemorial. While the exact time of its emergence is not known, it has been sufficiently demonstrated that a phytoplankton species *Emiliani huxleii*, which has existed unchanged in the Atlantic Ocean for more than 750 million years possessed the ability to make vitamin D when exposed to sunlight (Holick, 2003). Some researchers contend that the lack of sunlight-mediated vitamin D synthesis was triggered by the collision of steroids with Earth 65 million years ago - prompting the demise of dinosaurs (Holick, 2003). Others argue that bone-deforming and growth retarding diseases such as rickets were widened with the advent of industrialization. Nonetheless, all sides agree that exposure to ultraviolet radiation from the sun unequivocally prevents and cures rickets (Stoffers, et al., 2022); (Hess and Unger, 1921).

Although the first affirmative scientific relationship between rickets and vitamin D deficiency was initially identified by both (Whistler, 1645) and (Glisson, 1650), the consequential breakthrough in comprehending the causal factors of rickets was strengthened with the advancement of experimental science in nutrition and the appreciation of the existence of vitamins. Similarly, (Mellanby, 1921) devised an experimental diet that helped him to determine that bone-dense - rickets of indoor-raised dogs are caused by a deficiency of a trace component in the diet. This author also established that code liver is an excellent antirachitic agent (Mellanby, 1921). Also, Goldblatt and Soames identified a substance equivalent to the fat-soluble vitamins that are produced when a precursor of vitamin D in the skin (7-dehydrocholestrol) is irradiated with sunlight or ultraviolet light (Goldbalt and Soames, 1923). As well, Steenbock ascertained that rats' food with ultraviolet light acquired the property of being antirachitic (Steenbock, 1924).

The objective of such pronouncements was followed by determining the chemical structure of vitamin D by Adolf Otto Reinhold, the 1928 Nobel Prize winner of chemistry (Crowfoot-Hodgkin, 1957). Since the determination of the chemical structure of vitamin D_3 and vitamin D_2, there was an assumption that both vitamins have equal biological activities in humans. In fact, the postulation was crafted out of the comparative antirachitic activity revealed in rats. Conversely, the dietary reference intake for vitamin D defined serum 25-hydroxyvitamin D (25 (OH)D) as a functional indicator of vitamin D status than the antirachitic activity (Pludowski et al., 2002); (Whiting et al., 2011); (Langlois et al., 2010). It is possible to extrapolate that all experts agree that vitamin D normalizes the absorption of calcium and phosphorus in human bones and assists cell-to-cell communication in the body. The main objective of this review paper is to demonstrate the impact of vitamin D deficiencies on public health in general and on cold countries such as Canada in particular. More specifically, it is to raise awareness of the problem and to have a strategy for developing preventive measures.

METHODOLOGY

The method we used to conduct the review process is Document Analysis. This document analysis is based on Scott's (1990) principle. This principle has three criteria.

- **Originality** of the documents to be used. In this review, all the literature that we used are original articles.
- **Authenticity** of the document used. The authenticity of the articles used to prepare this review is ascertained.
- **Credibility** of the documents used. All articles used in this review are authored by known researchers. This can be proved by the references cited throughout the paper. All the materials used for writing this article regarding vitamin D are primarily gathered and sorted out based on their relevance to this point. In fact, the materials used are qualitative-based literature. A detailed analysis of the materials by classifying them into subtopics that compares and contrasts them was undertaken to elucidate the overall issues of vitamin D. Also, vitamin D materials were categorized based on their fit into Vitamin D2, and D3 that were the subject of our investigation.

Defining Vitamin D

Most experts agree that Vitamin D is a fat-soluble vitamin made in the body post-exposure to ultraviolet rays of the sun. Vitamin D is a hormone that sends messages to the intestine to maximize the absorption of calcium and phosphorus. By promoting calcium absorption, vitamin D boosts the maintenance of strong bones (Bacchetta et al, 2022). Thus, vitamin D increases bone mineralization, reinforces the immune system, normalizes cell growth, and prevents cancer (Muñoz and Grant, 2022). In effect, it prohibits the growth of anti-immune diseases such as inflammatory bowel disease, multiple sclerosis, and rheumatoid arthritis (Hess and Unger,1921). It is widely known that vitamin D can be generated from diets and the exposure of skin to sunlight (Hess and Unger, 1921). Five forms of vitamin D have been discovered, namely, vitamin D_1, D_2, D_3, D_4, and D_5. The most important forms of vitamin D in humans are vitamins D_2 (ergocalciferol) and D_3 (cholecalciferol) (Heaney et al., 2011). And only a few natural food sources contain a significant amount of vitamin D_2 and Vitamin D_3. Nonetheless, there is a plethora of logical raison d'être - emphasizing the vitality of vitamin D_3 over vitamin D_2 (Armas *et al.*, 2004).

The chemical structures of Vitamin D2, Vitamin D3, and the active form of Vitamin D are illustrated in (*Fig 1*) below (Novak, 1997)

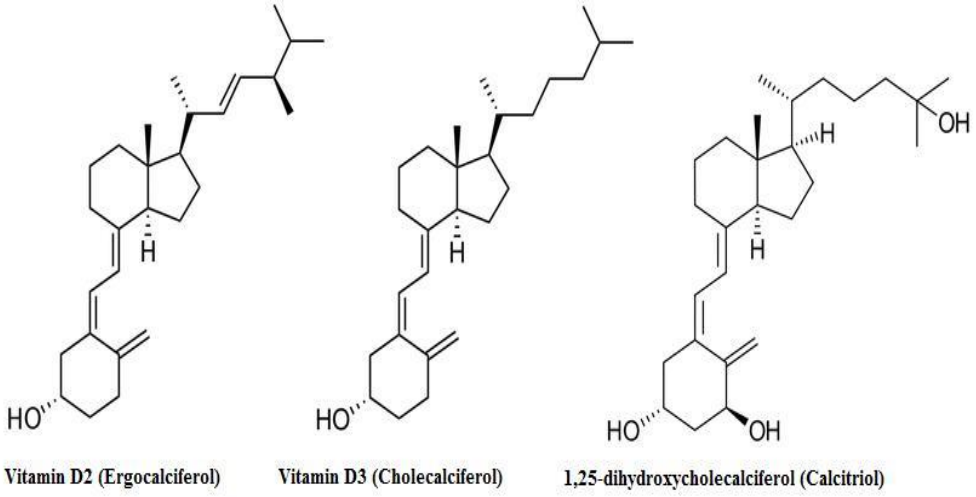

Fig 1: Chemical structure of vitamin D2, D3, and the active form of vitamin D

On the one hand, Vitamin D_3 is the most natural form of vitamin that can effectively raise and maintain vitamin D blood tests (Calverley and Jones, 1992). Cholecalciferol (Vitamin D_3) is the form of vitamin D produced when skin is exposed to UV B rays of sunlight. Most experts utilise this type of vitamin in clinical practice (Williams, 2022): (Wolpowitz and Gilchrest, 2006). The human body converts 7-dehydrocholestol through a series of biological steps to Cholecalciferol and this cholecalciferol is converted to calcifediol called 25-hydroxyvitamin D_3 (Crowfoot-Hodgkin, 1957). Finally, the human body changes calcifediol into the active form of vitamin D, calcitriol (Holick, 2006). On the other hand, (ergocalciferol) or Vitamin D_2 is a fungus/yeast-derived product that was first produced in the 1920s by exposing food to ultraviolet lights (Vitamin D Rapid Review, 2014). It is understood that vitamin D_2 is a white crystalline sterol produced by ultraviolet irradiation of ergosterol and also occurs naturally in fungi and some fish oils.

In comparison, vitamin D_3 is more stable and can remain active longer. And, it is clearly labeled to appropriate durations and satisfactions and is the most utilized form of vitamin D in clinical trials as opposed to vitamin D_2. R. Heaney and associates (Heaney et al., 2011) have explained that vitamin D_3 is approximately 87% more powerful in raising and maintaining serum 25 (OH)D levels than vitamin D_2. Given the lower cost and strength of vitamin D, the authors recommended that vitamin D_3 be the preferred choice for correcting vitamin D deficiencies. However, contemporary major prescription forms of vitamin D are that of vitamin D_2 component than vitamin D_3. Some people argue that taking too much vitamin D can lead to vitamin D toxicity (Jones, 2008). In particular, taking an excessive amount of vitamin D_3 in supplementation form can cause serious illnesses including liver and kidney disease. Therefore, any vitamin supplementation must be taken in moderation.

Vitamin D Sufficiency and Deficiency

Recently, multiple gauges have been employed to evaluate the deficiency, sufficiency/ insufficiency, and adequacy/ inadequacy of vitamin D in the human body. Many experts advised that vitamin D deficiency/insufficiency/adequacy are determined as less than 20, 21-29, and less than 30 ng/ml, respectively. In the absence of a sufficient level of exposure to sunlight, a minimum of 1000 IU of vitamin D_2 or vitamin D_3 should be taken daily (Malabanan, 1998): (Bertoldo et al, 2022). It is common knowledge that the deficiency of vitamin D is very critical in pregnant women and newborns (Lee et al., 2007), young and adolescent children (Sullivan et al., 2005), and middle-aged and older adults (McKenna, 1992). Also, vitamin D deficiency is very common in black people who do not get sufficient sunlight (Hess and Unger, 1921).

As the shortage of vitamin D can trigger growth retardation, skeletal deformities, and increased risk of hip fracture in children, it can also exacerbate osteopenia, osteoporosis, muscle weakness, common cancer, cardiovascular and autoimmune disease in adults (Holick, 2006) (Bertoldo et al., 2022). Without a proper vitamin D intake, only 10-15% of dietary calcium and about 60 % of phosphorous can be absorbed by the human body (Hess and Unger, 1921). Numerous studies have shown that people living at a higher altitude where the sunrise is unable to sufficiently produce an adequate amount of vitamin D in the skin are more likely to have increased mortality

from Hodgkin's, lymphoma, colon, pancreatic, prostate, ovarian, and breast cancers (Malabanan, 1998). Also, as people age, the skin cannot synthesize vitamin D efficiently, and the kidney can convert vitamin D to its active hormone form less (Salamone et al., 1993). Also, it is estimated that 30-40 per cent of older adults with hip fractures are insufficient vitamin D takers (Cauley et al., 2008). Therefore, acting through the VDR, $1,25(OH)_2D$ can produce various favorable biological effects that collectively improve human health.

The Consequence of Vitamin D Deficiency

Many experts emphasize that vitamin D deficiency causes significant medical and psychological impacts (Light et al., 1989). All tissues in the body, including the brain, heart, muscles, and immune system, have vitamin D receptors (VDR). Thus, vitamin D is very important in assisting the functions of all parts of the body (Qurban, 2022). As a hormone, it assists with the absorption of calcium to build strong bones, teeth, and muscles (Heaney, 2003). In addition, vitamin D activates genes that monitor the immune system and release neurotransmitters to shape brain function (Tsoukas et al., 1984); (Qurban, 2022). For many years, humans have tried to avoid exposure to the sun by wearing sun protection (Wolpowitz and Gilchrest, 2006). Even the lack of vitamin D was not considered a risk by some people who assumed acquiring vitamin D from dietary sources alone. However, most studies have revealed that fortified foods contain only 100 IU – an inadequate amount of vitamin D. Accordingly, if vitamin D deficiency is not properly addressed, it can easily set off the alarm of acute diseases as described below.

The most acute disease caused by the lack of vitamin D is Cancer. The correlation between sun exposure and cancer mortality was first noted by Hoffman in 1915 (Hoffman, 1915). Peller and Stephenson (Peller S, Stephenson C.S., 1937) advanced that people exposed to sufficient sunlight had decreased incidence of malignant tumors. (Apperly F.L, 1941) reported that people living at high altitudes die from cancer more than people living at low altitudes. (Garland et al., 1990) and (Goraham et al, 2007) have concluded that there is a negative association between latitude, sun exposure, and poor vitamin D status – followed by deadly cancers such as colon, breast, ovarian and melanoma. Also, (Grant W.B., 2002) pointed out that several types of cancer were reduced by adequate exposure to solar ultraviolet B radiation (Muñoz, A. and Grant, W.B., 2022). It is clear that $1,25(OH)_2D_3$ is one of the most active hormones for inhibiting both normal and cancer cell proliferation and inducing maturation (Holick M.F, 2007). Hence, a large number of genes control proliferation, differentiation, apoptosis, and angiogenesis that are either directly or indirectly influenced by $1,25(OH)_2D_3$ (Krishnam, 2003). The $1,25\ (OH)_2D_3$ increases inhibitors and decreases activators of cyclin-cyclin dependent Kinase inhibitors Cip/Kip proteins-P21 and P27. These proteins keep the cell cycle in the G1/S phase, preventing cellular growth (Spina et al., 2006).

It is widely argued that the colon cancer cell line exposed to the vitamin D receptor (VDR) HT-29 responded to $1,25\ (OH)_2\ D_3$ by a dosage-dependent inhabitation of cellular growth and induction of differentiation (Swami, 2003); and (Mohd et al, 2022). Various tumor cell lines – leukemia, melanoma, lung, breast, and prostate cancer cells have adequately responded to the proliferating activity of $1,25\ (OH)_2\ D_3$ (Gorham, 1989). Moreover, $1,25\ (OH)_2$ D3-induced apoptosis is antiangiogenic in vivo and vitro. The majority of human colorectal cancer cases are sporadic and their incidences are highly associated with age, nutrition, and lifestyle. Various experts (Swami, 2003); (Gorham, 1989) have reiterated the prevalence of inverse correlation between exposure to solar radiation and the development of carcinoma of breast cancer, colon (Garland, 1980), NHL (Hartge, 1996), and prostate (Hanchette and Schwartz, 1992).

In short, all experts concur that exposure to solar ultraviolet (UV) – B radiation reduces the risk of cancer through the photoinitiation of vitamin D production. Moreover, the Canadian cancer society recommends that adults ingest 2000 IU/day of vitamin D to decrease cancer risk (Muñoz and Grant, 2022). Furthermore, the Canadian dermatologic association, the US national council on skin cancer, and the world health organization have minimized the risk associated with excessive UV B radiation (Holick, 2008).

The other disease that may attack people due to the lack of vitamin D is asthma: The lack of vitamin D in children has been viewed as a precursor to asthma symptoms. Appropriate vitamin D intake can quell the inflammation that restricts airways from proper breathing (Poon et al., 2004). Epidemiological studies have suggested that higher prenatal vitamin D intakes have a protective role against wheezing illness (Sherchand et al., 2022). Adequate Vitamin D intakes minimize wheezing by regulating antimicrobial proteins through its multiple immune effects. Therefore, a low vitamin D level is associated with a high risk of exacerbating asthma (Litonjua and Weiss, 2007).

In addition, Inflammatory Bowel Disease is also considered the byproduct of vitamin D deficiency. Various studies have shown that there is a link between low vitamin D intake and a higher rate of Crohn's disease and ulcerative colitis (Wilson et al., 2010). These studies assert that a population with low sunlight exposure has a high rate of inflammation with strong mucosal barriers (Loftus, 2004). Crohn's disease is an inflammatory disease of the intestinal tract. This disease causes the thickening of the intestinal wall and

inflammation of the intestinal lining - leading to abdominal pain, diarrhoea, and weight loss (Siffledeen et al., 2003). Ulcerative colitis is another chronic colon inflammation that produces ulcers in its lining. Its symptom is marked by abdominal pain and cramps (Moum, 1996). The marker of vitamin D, 25-hydroxyvitamin D (25(OH)D) modulates vascular inflammation (Holick and Chen, 2008).

Furthermore, hypertension is another negative implication of vitamin D deficiency. This disease is related to high blood pressure; transitory or sustained elevation of systemic arterial blood pressure to a level likely to induce cardiovascular damage or other adverse consequences. Boosting the level of vitamin D intake reduces the magnitude of hypertension. (Rostand, 1979) reported that people living at higher latitudes throughout the world have higher hypertension risks. Additionally, the precursor of Type 2 diabetes is the shortage of vitamin D. Vitamin D scarcity can exacerbate the symptom of metabolic syndrome in patients with HIV (Raloff, 2004): (Qurban, 2022). Thus, maintaining high vitamin D levels via exposure to sunlight or supplementations can sharply minimize the risk of developing type 2 diabetes (Mitri et al., 2011). As well, influenza is a common disease instigated by vitamin D deficiency. Influenza is a viral infection of the lung causing headache, fatigue, sore throat, dry cough, muscle pain, and fever (Britten, 1932). The rates of influenza are higher in winter when there is no much sunlight and ultraviolet B rays. The population should take sufficient vitamin D to boost their immune system during winter (Aloia and Li-Ng, 2007). Many randomized controlled trials have indicated that people taking an adequate level of vitamin D encounter a reduced incidence of influenza (Cannell et al., 2008).

It is also proven that poor dental health can be caused by a lack of vitamin D. Optimal vitamin D levels promote the healthy calcification of teeth. Many studies were conducted in the 1930s and 1940s (McBeath, 1938). and more than 90% of them concluded that supplementing children with vitamin D prevents cavities. Particularly, an impressive study was published in 1941 demonstrating the preventative effect of a massive dose of vitamin D. Yet no subsequent study could replicate it (Brodsky, 1941). And, Rheumatoid Arthritis is another serious disease that has a considerable association with vitamin D deficiency. Those people with low blood plasma levels of 25(OH)D are five times more susceptible to RA diseases (Costenbader et al., 2008); Chakkera et al., 2022).

Generally, it is believed that vitamin D and calcium insufficiency instigate the development of colon cancer (Lamprecht and Lipkin, 2003). Several pieces of evidence have clearly shown that calcium and vitamin D status usually act together to monitor colon epithelial cell proliferation (Peterlik and Cross, 2005). Nonetheless, calcium supplementation can be effective only in patients with physiological normal 25(OH)D_3 concentration. The interaction between nutritional calcium and vitamin D to protect against colorectal cancer may be due to the ability of luminal calcium to suppress the degradation of 1,25 $(OH)_2$ D_3 synthesized in colonocytes (Hartman, 2005).

Intersectionality of Ecology, Season, and Vitamin D

Cancer-related mortality rates vary across regions (Grant, 2001). In some areas, exposure to sunlight provides humans with vitamin D. In other areas, cloud covers, smokes, and sunscreens affect UV ray exposure and vitamin D synthesis. Moreover, most adults who work indoors during day times miss sun lights. Hence the sunscreen blocking UV rays instigates the endemic of vitamin D deficiency (Holick and Chen, 2008).

The most risk factor for cancer is the environment (Gorham, 1990) with diet and lifestyle choices of smoking playing the largest role. Low 25(OH)D_3 levels are also seen with housebound or hospitalized elderly - older people are prone to colorectal cancer. For this reason, (Garland, 1980) proposed vitamin D as a protective factor against colorectal cancer. They arrived at this conclusion by observing the high mortality of people unexposed to solar radiation. The concentration of 25 (OH) D_3 in the blood varies between 25 and 125 nmol/L in winter and 50 -200 nmol/L in summer (Dawson-Hughes, 1997).

Sources of Vitamin D and Metabolism

Very little vitamin D is naturally present in regular foods. An oily fish, including salmon, mackerel, herring, cod liver oil, and sun-dried mushrooms, typically provide 400–500 IU of vitamin D per serving (Nakamura et al., 2000); (Kame et al., 2022). As discussed earlier, Cholecalciferol (vitamin D_3) is produced in the skin post-sun exposure and 90–95% of most people's vitamin D requirement comes from casual sun exposure. 7-dehydrocholesterol is extracted from wool fat and commercially produced and then exposed to UVB irradiation and purification (Heaney et al., 2011): (Holick, 2002). The transformation mechanism of Vitamin D2 and Vitamin D3 is illustrated in (*Fig* 2) as follows (Chilaya et al., 2005)

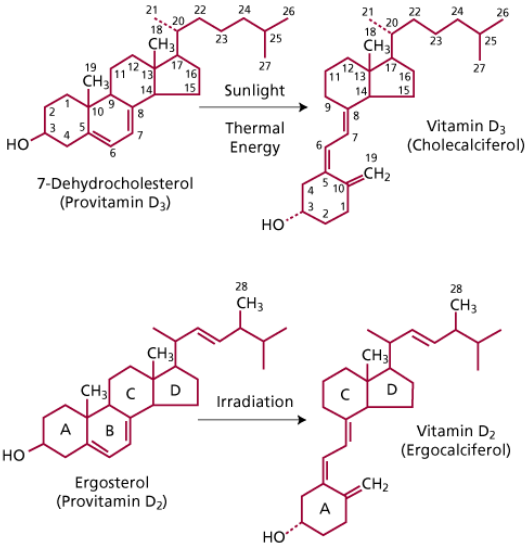

Fig 2: Vitamin D2 and Vitamin D3 Transformation

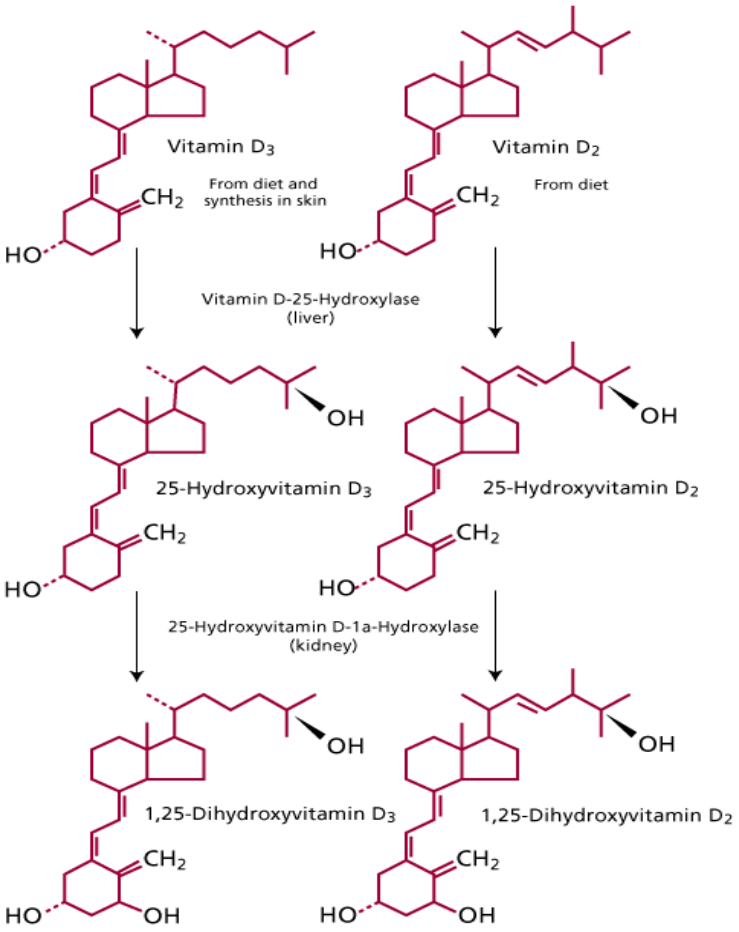

Figure 3: Metabolism of Vitamin D3 and Vitamin D2

Ergocalciferol (vitamin D_2) has a different side chain than cholecalciferol (vitamin D_3) i.e., a C_{24} methyl group and a double bond between C_{22} and C_{23} and is commercially made by irradiating and then purifying the ergosterol extracted from yeast (*see Fig* 2). Fish oil is an excellent nutritional source of vitamin D (Dawson-Hughes, 1997). Recently, however, it has been reduced due to changes in lifestyles in many countries including Canada. The metabolism of Vitamin D2 and Vitamin D3 in our body (Liver and Kidney) is illustrated schematically in (*Fig*.3) (Jones, 2013).

In the liver, vitamin D is hydroxylated to 25-hydroxycholecalciferol ($25(OH)D_3$) (Gorham *et al*., 1989), the major circulating form of steroid. The $25(OH)D_3$ has no intrinsic biological activity, but it serves as the substrate for hydroxylation and can be considered a prohormone (Dawson-Hughes *et al*., 1997).

Finally, 25(OH)D or calcifediol is converted into the active form of vitamin D, calcitriol, or 1,25 (OH)2 D in the kidney (Holick, 2006). A Serum level of $25(OH)D_3$ is a direct reflection of sunlight exposure, the use of sun blockers, and skin pigmentation. Hence, exposure of the skin to the UV B rays of the sun induces the photolytic conversion of 7-dehydrocholesterol to pre-vitamin D, later ensued by the terminal isomatization to vitamin D_3 (Okano *et al*., 1977).

Social Policy and Vitamin D

Various policymakers spend magnanimous time discussing how to reduce hospital waiting times. However, what is missing from the dialogue is how to minimize the entire hospital visitation by strictly enlightening the public about the contribution of vitamin D to a healthy life. Also, there is no much debate on the exposure of children to adequate sunlight. Such a discussion would have enabled policymakers to enact a mature preventive policy that creates a healthy future. The public must also be receptive to such important educative interventions from policymakers to raise children in a collaborative fashion.

This grand social venture should not be left to Health Canada alone but rather be embraced by all departments, agencies, and actors. In fact, Health Canada has a role in prevention via its regulatory authority - it can monitor the quality of drugs, evaluate applications and give licenses to drug companies as well as oversee the ethics and the code of medical provisions to Canadians. Here, some may argue that the involvement of more levels of government and departments creates redundancies. In terms of educating the public, however, there are no redundancies but only concurrences. Raising public awareness about vitamin D must be part of the basic package of Canadian national healthcare and the government should allocate resources to raising awareness as a part of public health and safety. The fact that Canada does not look to the individual patient as an agent of health cost control is conducive enough in itself for vitamin D-related awareness-raising efforts.

The Role of Social Institutions

Some social institutions have a critical responsibility to help the public understand the stake of not properly and adequately taking vitamin D. These institutions have social and ethical tasks of promoting preventive care. Most importantly, religious institutions have to play a critical role in educating the public about the importance of Vitamin D. The assumption that some diseases come due to the wrath of God should temporarily be set aside. Instead, corrective and protective means of education have to be rearranged. As congregants look for guidance from religious leaders, the leaders should take the opportunity to teach the masses (Regnerus, 2003). Also, some advocacy agencies that usually endeavor to promote social justice should embrace the idea of individual health. As they project corrective remedies to abusive relationships, they must also consider fighting against abusive diseases to realize the dream of a healthy society. Justice requires a commitment to health as justice demands a tangible, long-term pledge to public health (Powers and Faden, 2006). Also, precollege schools should develop curriculums that make vitamin D a core program so that all students take it seriously. All students must be indoctrinated that knowing about vitamin D and adequately taking it is the cornerstone of a healthy and happy future (Jeanne et al., 2008).

In particular, mass media is expected to pay closer attention to the transmission of vitamin D education. Media should advocate civic engagement by creating a medium of social conversation and dialogue on vitamin D (Considine, 1995). They should invite experts on vitamin D to shade light on the importance of vitamin D. Generally, promoting vitamin D intake is the basic instrument to protect people from untimely deaths and malicious chronic diseases, and, family as a cornerstone of society must play a pivotal role in choosing the proper diet for their children. All families should give vital vitamin D to children to strengthen their bones. A strong bone is the best wall that carries children throughout their lives. Various experts recommend that all families expose their children to sunlight for usually no more than 5–15 min/d (between 10 AM and 3 PM) on arms and legs or hands, face and arms, during the spring, the summer, and the fall to provide the body with its required 1000 IU of cholecalciferol (Gorham et al., 1989). Hence, the ideal health care thrives not only on cures but mostly on prevention. In comparison, prevention strategy is less costly, tension-free, and its results are positively predictable. In short, vitamin D is a colossal weapon in the arsenal of preventive health. For these reasons, promoting vitamin D intake should be treated as a source of social security and public

welfare. Besides recommending vitamin D intake, Health Canada can do more, including organizing seminars, writing memos to all institutions, and encouraging media to promote vitamin D intake.

CONCLUSION

The importance of vitamin D has immensely captured the imagination of researchers and healthcare professionals. It has become the bludgeon for preserving calcium metabolism and good skeletal health. Also, it is accepted as a means of regulating blood pressure, controlling cancer cell growth, and normalizing the immune system. Thus, sufficient vitamin D intake is crucial to prevent chronic diseases that can seriously affect children and adults. A lack of vitamin D poses a series of health threats, so it should be routinely checked during physical examination. Therefore, besides reasonable sun exposure, selected vitamin D-fortified foods should be taken seriously to maximize good health.

REFERENCES

Aloia, J. F. Li-Ng, M. 2007. Epedemic influenza and vitamin D, Epidemiol Infect, *Midline*. 135 (7):1095-6

Apperly, F.L: 1941. The relation of solar radiation to cancer mortality in North America. *Cancer Res* 1,191–195.

Armas, LA, Hollis B.W, Heaney R.P. 2004. "Vitamin D2 is much less effective than vitamin D3 in humans." *J Clin Endocrinol Metab*. Nov;89(11):5387-91.

Bacchetta, J. Edouard, T., Laverny, G., Bernardor, J. *et al*, 2022.Vitamin D and calcium intakes in general pediatric populations: A French expert consensus paper, *Archives de pediatrie* 1-14.

Bertoldo, F. Cianferotti, l., Di Monaco, M., Falchetti, A. *et al*, 2022. Definition, Assessment, and Management of Vitamin D Inadequacy: Suggestions, Recommendations, and Warnings from the Italian Society for Osteoporosis, Mineral Metabolism and Bone Diseases (SIOMMMS), *Nutrients*, 14, 4148.

Britten, R. H.1932.The incidence of endemic influenza. 1918-19. *Pub Health Rep*. 47303-39.

Brodsky, R. H.; 1941., Schick, B.; Vollmer, H. Prevention of dental caries by massive doses of Vitamin D. *American Journal of Diseases of Children* 62, 1183-7.

Calverley, M.J. and Jones, G. 1992.Vitamin D In Antitumor Steroids, edited by Blicknstaff, R.T. *San Diego Academic Press,* pp 193-270.

Cannell, J. J. Zasloff, M. Garland *et al*, 2008. On the epidemiology of influenza. *Virol J*., Feb 25 (5): 29.

Cauley, J.A, Lacroix, AZ., Wu, l., Horwitz, M. *et al*. 2008. Serum 25-hydroxyvitamin D concentrations and risk for hip fractures. *Ann Intern Med.,* Aug; 149(4), 242-50.

Chakkera, M. Ravi, N., Ramaraju, R., Vats, A., Nair, AR. *et al*, 2022.The Efficacy of Vitamin D Supplementation in Patients with Alzheimer's Disease in Preventing Cognitive Decline: A Systematic Review, *Cureus* 14.

Chilaya, G., Petriashvili, G., Chanishvili, A., Terenetskaya, I., Kireeva, N., Lisetski, L., 2005, Provitamin D2 and Provitamin D3 Photo Transformations in Cholesteric Liquid Crystal Mixtures Induced by UV Radiation, *Mol. Cryst. Liq. Cryst*., 433, 73-85

Costenbader K., Feskanich D., *et al*, 2008. Vitamin D intake and risks of systemic lupus erythematosus and rheumatoid arthritis in women. *Ann Rheum Dis* 67: 530–535.

Considine, D. M. 1995.Are we there yet? An update on the media literacy movement, *Educational Technology*, 35 (4), 32-43.

Crowfoot-Hodgkin, D., 1957. Structure of calciferol. *Chem. Industry,* 1148-1149.

Dawson-Hughes B, Harris S.S, 1997.Plasma calcidiol, season, and serum parathyroid hormone concentrations in healthy elderly men and women. *Am J Clin Nutr*, 65, 67–71.

Garland FC., Garland CF., Gorham, E., Young JF., 1990. Geographic variation in breast cancer mortality in the United States: A hypothesis involving exposure to solar radiation. *Prev Med* 19, 614–622.

Garland, C.F.and Garland F.C. 1980.Do sunlight and vitamin D reduce the likelihood of colon cancer? *Int J Epidemiol*. 9, 227–231.

Glisson, F. 1650. De Rachitide sive morbo puerili, qui vulgo The Rickets diciteur, London 1- 416.

Goldbalt, H. and Soames, KN. 1923. A study of rats on a normal diet irradiated daily by mercury vapor quartz lamp or kept in darkness. *Biochem.J.* 17, 294-297.

Gorham, E.D, Garland C.F, Garland, FC., Grant WB., Mohr, SB. *et al*; 2007. Optimal vitamin D status for colorectal cancer prevention: A quantitative meta-analysis. *Am J Prev Med* 32, 210–216,

Gorham, E.D, Garland F.C, 1990. Sunlight and breast cancer incidence in the USSR. *Int J Epidemiol.* 19, 820– 824.

Gorham, E.D, Garland C.F, 1989. Acid haze air pollution and breast and colon cancer mortality in 20 Canadian cities. *Can J Public Health,* 80, 96–100,

Grant W.B. 2001.An ecologic study of the role of solar UV-B radiation in reducing the risk of cancer using cancer mortality data, dietary supply data and latitude for European countries. In: Holick M.F, (editor.), Biologic effects of light 2001.

Grant, W.B: 2002. An estimate of premature cancer mortality in the US due to inadequate doses of solar ultraviolet-B radiation. *Cancer* 94, 1867–1875.

Hanchette, C.L, Schwartz G.G., 1992.Geographic patterns of prostate cancer mortality.*Cancer*, 70: 2861-2869.

Hartman, T.J, Albert P.S,*l*, 2005, The association of calcium and vitamin D with risk of colorectal adenomas. *J Nutr*. 135, 252–59.

Hartge P, Devessa *l*, 1996.Non-Hodgkin's lymphoma and sunlight. *J Natl Cancer Inst*. 88, 298–300.

Heaney, R.P and Dowell M.S, 2003. Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D. *J Am Coll Nutr,* 22, 142-146.

Heaney, R.P., Recker, R.R., Grote, J., Horst, RL., Armas, LAG., 2011. Vitamin D3 is more potent than VitaminD2 in humans. *J. Clin.End. Metab* , 93: 447-452.

Hess, A.F, Unger L.J: 1921. The cure of infantile rickets by sunlight. *JAMA* 77, 39–41.

Hoffman, F.L: 1915. The Mortality of Cancer throughout the World, *New York, Prudential Press*.

Holick, M.F. 2002.Vitamin D: the underappreciated D-lightful hormone that is important for skeletal and cellular health. *Curr Opin Endocrinol Diabetes,* .9, 87-98.

Holick, M.F: 2003. Vitamin D: A millennium perspective. *J Cell Biochem* 88, 296–307.

Holick, M.F: 2006. Resurrection of vitamin D deficiency and rickets. *J Clin Invest* 116, 2062–2072.

Holick, M.F: 2007. Vitamin D deficiency. *N Engl J Med,* 357, 266– 281.

Holick, M.F. 2008. Vitamin D and Sunlight: Strategy of Cancer Prevention and Other Health benefits. *Clin J Am Soc Nephrol 3*, 1548–1554.

Holick M.F, Chen T.C., 2008. Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr.* 87,1080S–1086S,

Jeanne, H, *et al*. 2008. School and Society – A Sociological Journey to Education. Thousand Oaks, *Pine Forge Press.*

Jones, G. 2008. Pharmacokinetics of vitamin D toxicity. *Am J Clin Nutr*, 88: 582S–6S.

Jones, G., 2013. Extrarenal Vitamin D Activation and Interactions Between Vitamin D2, Vitamin D3, and Vitamin D Analog, Annu. Rev. Nutr. 33:23–44

Kame, S.M., *et al*, 2022. Evaluation of Vitamin D_3 Content in Selected Dried, Canned and Smoked Fish, *J Nutri Med Diet Care*, 8, 56.

Krishnam AV, Peehl D.M, Feldman D: 2003. The role of vitamin D in prostate cancer: Recent results. *Cancer Res* 164, 205–221.

Lamprecht, SA, Lipkin M. 2003. Chemoprevention of colon cancer by calcium, vitamin D and folate: molecular mechanisms. *Nat Rev Cancer*. 3, 601–14.

Langlois, K, Greene-Finestone L., Little, J., Hidiroglou, N., Whiting, S., 2010. Vitamin D status of Canadians as measured in the 2007 to 2009 Canadian Health Measures Survey. Health Reports, March 2010; Catalogue no 82-003-X

Lee J.M, Smith J. R, Philipp, BL., Chen, TC., Mathieu, J., Holick, MF., 2007. Vitamin D deficiency in a healthy group of mothers and newborn infants. *Clin Pediatr* , 46: 42–44.

Litonjua, AA, Weiss ST. 2007. Is Vitamin D Deficiency to Blame for the Asthma Epidemic? *J Allergy Clin Immunol*. 120, 1031-5.

Loftus, EV Jr. 2004. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology*, 126 (6), 1504–1517.

Malabanan A, Veronikis IE, Holick M: F: 1998.Redefining vitamin D insufficiency. *Lancet,* 351, 805–806.

McBeath, E.C. 1938. Nutrition and diet in relation to preventive dentistry. *NY J. Dentistry*, 8, 17-21.

McKenna M.J: 1992. Differences in vitamin D status between countries in young adults and the elderly. *Am J Med* 93, 69–77.

Mellanby, E. 1921. Experimental rickets. Medical research (G.B.), Special report Series SRS-61, 1-78.

Mitri, J, Muraru, MD., Pittas, AG. 2011. Vitamin D and type 2 diabetes: a systematic review. *Eur J Clin Nutr*. July 6

Mohd, A., 2022. Vitamin D as a drug: new therapeutic approaches, *Pharmacia* 69, 765–770.

Moum, B, Aadland E., 1996. Seasonal variations in the onset of ulcerative colitis. *Gut,* 38, 376–8.

Muñoz, A. and Grant, W.B., 2022. Vitamin D and Cancer: An Historical Overview of the Epidemiology and Mechanisms *Nutrients* 14, 1448.

Nakamura K, Nashimoto M, *et al*, 2000. Serum 25-hydroxyvitamin D concentrations and related dietary factors in peri- and postmenopausal Japanese women. *Am J Clin Nutr*, 71, 1161–65.

Nova, I. and Potts, AW. 1997.Electronic Structure of Vitamin D2 and Vitamin D3, *Biochimica et Biophysica Acta*, 1319, 86-90

Okano, T, Yasumura M, *et al*, 1977.Photochemical conversion of 7-dehydrocholesterol into vitamin D3 in rat skins. *J Nutr Sci Vitaminol,* 23, 165–168.

Peller S, Stephenson C.S: 1937. Skin irritation and cancer in the United States Navy. *Am J Med Sci* 194, 326–333.

Peterlik, M, Cross H.S. 2005. Vitamin D, and calcium deficits predispose for multiple chronic diseases. *Eur J Clin Invest*. 35:290–304.

Pludowski, P., *et al*, 2022. Clinical Practice in the Prevention, Diagnosis and Treatment of Vitamin D Deficiency: A Central and Eastern European Expert Consensus Statement, *Nutrients*, 14, 1483.

Poon, A.H, Laprise C, Lemire M, *et al*. 2004. Association of Vitamin D Receptor Genetic Variants with Susceptibility to Asthma and Atopy. *Am J Resp Crit Care Med*. 170, 967-973.

Powers, M. and Faden R. 2006. Social Justice: The Moral Foundations of Public Health and Health Policy (New York): *Oxford University Press*.

Qurban, R., 2022.Potential immune modulatory effect of vitamin D in HIV infection: A review, *Clinical Nutrition ESPEN,* 47, 1-8.

Raloff, J.; 2004. "Vitamin D and HIV"; *Science Magazine*; 16 Oct; Vol 166, No.16.

Regnerus, M.D. 2003. Religion and positive adolescent outcomes: A review of research and theory, *Review of Religious Research*, 44, 394-413.

Rostand, S.G. 1979.Ultraviolet light may contribute to geographic and racial blood pressure differences. *Hypertension*, 30:150-156.

Salamone, L.M. 1993.Contributions of vitamin D intake and seasonal sunlight exposure to plasma 25-hydroxyvitamin D concentration in elderly women. *Am J Clin Nutr,* 58, 80-86.

Sherchand, O., *et al*, 2022. Epidemiology and Determinants of Vitamin D Deficiency in Eastern Nepal: A Community-Based, Cross-Sectional Study, *International Journal of Endocrinology,*

Siffledeen, J.S, Siminoski K, *et al*, 2003. The frequency of vitamin D deficiency in adults with Crohn's disease. *Can J Gastroenterol* ,17, 473–8.

Spina, C.S, Tangpricha V, *et al,* 2006. Vitamin D and cancer. *Anticancer Res* 26, 2515–2524.

Steenbock, H. 1924, The induction of growth promoting and calcifying properties in a ration by exposure to light. *Science,* 60, 224-225.

Stoffers, A. J., *et al*, 2022. An Update on Vitamin D Deficiency in the twenty-first century: nature and nurture, *Curr Opin*. 29, 36–43.

Stumpf W.E Privette T. H, Light, 1989. Vitamin D and psychiatry: role of 1,25-dihydroxyvitamin D_3 (soltriol) in etiology and therapy of seasonal affective disorder and other mental processes. *Psychopharmacology (Berl)*, 97 (3) 285- 294.

Sullivan, S.S, Rosen C.J, *et al*, 2005. Adolescent girls in Maine at risk for vitamin D insufficiency. *J Am Diet Assoc,* 105, 971–974.

Swami, S, Raghavachari M, *et al*, 2003. Vitamin D growth inhibition of breast cancer cells: Gene expression patterns expressed by cDNA microarray. *Breast Cancer Res Treat* 80, 49–62.

Tsoukas C.D, Provvedine D.M, *et al*, 1984. 125-Dihydroxyvitamin D_3, a novel immuno-regulatory hormone. *Science*, 221, 1438-1440.

Whistler, D. 1645. Morbo puerili Anglorum, quem patrio idiomate indigenae vocant: The Rickets. Lugduni Batavorum 1-13.

Whiting, S.J, Langlois K.A, *et al*, .2011. The vitamin D status of Canadians relative to the 2011 Dietary Reference Intakes: An examination in children and adults with and without supplement use. *Am J Clin Nutr,* Jul;94(1): 128-35.

Williams, S. E., 2022. Vitamin D supplementation: Pearls for practicing clinicians, *Cleveland clinic journal of medicine,* 89.

Wilson, J. Hair C, Knight R,*et al.* 2010. High incidence of inflammatory bowel disease in Australia: a prospective population-based Australian incidence study. *Inflamm Bowel Dis* 16, 1550–6.

Wolpowitz, D, and Gilchrest B.A. 2006. "The vitamin D questions: how much do you need and how should you get it?" *Journal of the American Academy of Dermatology*, 54, 301-317.