

Vitamin D Deficiency and its Repletion: A Review of Current Knowledge and Consensus Recommendations

Haroon M* and Fitzgerald O

Department of Rheumatology, St. Vincent's University Hospital, Ireland

Abstract

In last few years we have witnessed an explosion of research revealing the wide spread prevalence of vitamin D deficiency among all ages, communities, and different disease spectrums. Clearly, vitamin D has been shown to have effects beyond its traditional role in mineral metabolisms, which are mediated through the activation of vitamin D receptors distributed in a variety of tissues. There are strong epidemiological links between vitamin D deficiency and chronic diseases and will continue to be a focus of future research. However, this research information has not yet been fully translated into clinical practice. The increased awareness of the level of vitamin D deficiency in the general population and its potential impact on skeletal and extra skeletal health outcomes have highlighted the important need to understand and follow the latest research knowledge in this area. There remains a poor understanding among health professionals as regards the prescribing policy and the provision of appropriate vitamin D supplements. This review will discuss the physiological role of vitamin D, and the available literature on vitamin D deficiency with respect to its definition, associated factors, prevalence, and management recommendations, and the safety of its repletion.

Key words: Vitamin D; Deficiency; Repletion

Introduction

Our knowledge regarding the physiological role of vitamin D has significantly advanced during last few decades. There have been strides in the development of strategies to prevent and treat the deficiency of this natural hormone – vitamin D; however, vitamin D deficiency remains under recognised and untreated. Vitamin D is a seco-steroid hormone with one endocrine function – calcium regulation- but with multiple autocrine functions. The principal function of vitamin D is to control calcium metabolism, and its deficiency impacts the quality and quantity of bone formation by affecting calcium absorption. Besides its effects on musculoskeletal system, 1,25-dihydroxyvitamin D inhibits cellular growth, stimulates insulin secretion, modulates immune function, and inhibits renin production. These findings most likely explain the observations that vitamin D deficient people are more prone to solid tumours, autoimmune diseases and hypertension [1]; however, discussing such health consequences is beyond the scope of this paper.

Basic Physiology and Molecular Biology

To understand the importance of vitamin D, we need to understand its physiology. Vitamin D is a steroid hormone, and there are 2 forms of vitamin D - vitamin D₂ (known as ergocalciferol) and vitamin D₃ (named as cholecalciferol). Vitamin D₂ is a plant extract and Vitamin D₃ is synthesized by humans in the skin, when it is exposed to ultraviolet-B (UVB) rays from sunlight. Vitamin D is further hydroxylated in the liver to 25 hydroxyvitamin D (25OH vitamin D), which can accumulate in certain tissues. 25-OH vitamin D is the predominant circulating form of vitamin D in the blood and because of its close regulation by the availability of vitamin D, measurement of 25(OH) vitamin D is the most reliable indicator of vitamin D status. The active form, 1,25 dihydroxyvitamin D, is formed by subsequent hydroxylation in the kidney, and its half-life is very short (<4 hours). The renal hydroxylation is very closely regulated: enhanced by PTH, hypocalcaemia and hypophosphataemia and inhibited by 1,25(OH)₂D itself [2]. 1,25(OH)₂D is the principal hormonal form of vitamin D, responsible for most of its biologic actions. Molecular mechanisms of action of 1,25-dihydroxyvitamin D include genomic and non-genomic

effects [3]. Genomic effects of vitamin D are mediated by classical gene transcription or protein synthesis route, which is initiated by binding of 1,25(OH)₂D to its nuclear high-affinity vitamin D receptor (VDR) [4,5], which results in changes in the gene transcription of mRNA and subsequent de novo protein synthesis [6]. However, non-genomic functions of vitamin D are generally rapid responses (minutes to hours). Many of these rapid responses are believed to be mediated by 1,25D binding to a plasma membrane-associated receptor [3,7], which in turn, initiates a cascade leading to the formation of a second messenger (cAMP, diacylglycerol, inositol triphosphate, arachidonic acid) or phosphorylation of intracellular proteins. Such receptors are located in classical target organs involved in vital calcemic actions of vitamin D, such as the intestine, bone, kidney and parathyroid, as well as in many other tissues and cell types [2], including the immune system [8]. However, such non-genomic actions of vitamin D have not been demonstrated in vivo. The main biologic actions of 1,25-(OH)₂ vitamin D are: absorption of calcium from intestine leading to the mineralization of bone matrix; osteoblast differentiation; and inhibition of parathyroid hormone secretion. In calcium deficiency states, 1,25(OH)₂D mobilizes calcium stores from the bone through stimulation of monocytic cells to become mature osteoclasts, and thus, helps to maintain the serum calcium in the normal range [9]. Similarly, when vitamin D levels are low, compensatory secondary hyperparathyroidism increases the renal conversion of 25OHD and thereby maintains normal or slightly increased plasma levels of 1,25(OH)₂D. Moreover, this active form of vitamin D is stored in the adipose tissue rather than remains in the circulation and, therefore, is not a good measure of vitamin D status

*Corresponding author: Dr. Muhammad Haroon, Department of Rheumatology, St Vincent's University Hospital, Elm Park, Dublin 4, Ireland, E-mail: mharoon301@hotmail.com

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in serum. Both 25OHD and 1,25(OH)₂D undergo a 24-hydroxylation [10], which represents the first step in the biodegradation which ends with the formation of water-soluble calcitroic acid.

Factors Associated With Vitamin D Deficiency

Poor intake

There are multiple reasons for vitamin D deficiency. An important cause of vitamin D deficiency can be insufficient intake of dietary vitamin D. Extremely few foods naturally contain vitamin D, apart from oily fish in the form of salmon, mackerel, and sardines which are relatively rich in vitamin D₃. Similarly, only a small number of foods are fortified with vitamin D such as milk, orange juice and some bread and cereals. Such fortification is used in many developed countries [11]. In Europe, margarine, vegetable oil and milk are commonly fortified, whereas in the USA, enrichment of flour, cornflakes, milk and juice is common practice. It is important to note here that >90% of our vitamin D requirements come from sunlight exposure [12]. The average increment in serum 25(OH) D concentrations has been estimated at 1–2 nmol/L for every 40 IU (1 microgram) of vitamin D₃ depending on baseline 25(OH)D concentrations. Generally, the two forms of vitamin D, D₂ (ergocalciferol) and D₃ (cholecalciferol), are considered equivalent [13–15]. However, using 25(OH) D as an objective measure of response to vitamin D administration has shown that vitamin D₃ is a more potent form of vitamin D compared to vitamin D₂. Hence, some experts suggest that vitamin D₂ should not be used for supplementation or fortification [16]. A recent systematic review examined the effects of food fortification on circulating 25(OH)D concentrations by reviewing 13 randomised controlled trials. This showed a consistently positive response of dietary vitamin D supplementation among young adults, postmenopausal women and elderly men [17]. There is also some suggestion that this treatment effect is dependent on baseline 25 (OH) vitamin D levels, as the trials with low baseline 25(OH)D levels (i.e., <50 nmol/L) [18–21] have consistently demonstrated a greater percent increase in 25(OH)D levels at the end of study compared to trials with higher baseline 25(OH)D levels (i.e., >50 nmol/L) [22–25].

Poor production, malabsorption and obesity

Factors that can prevent exposure to sunlight are crucial in causing vitamin D deficiency. Such factors include: aging (which causes decreased dermal production through atrophic skin changes and decreased renal production of 1,25(OH)₂ vitamin D by diminishing renal function), changes in latitude, time of the day, and life style factors, such as limited outdoor activity, can have a marked influence on the cutaneous production of vitamin D. Similarly, any hindrance to ultraviolet sunlight exposure onto the skin in the form of either sunscreen use or increased melanin pigmentation (dark skinned individuals) can potentially cause vitamin D deficiency. Vitamin D deficiency is also more common in adults who cover their skin for cultural reasons [26–29]. A systematic review found that the risk factors for vitamin D inadequacy most often found in post-menopausal women include poor sun exposure, limited time spent outdoors, inadequate dietary vitamin D intake, winter season and increased age [30]. Another important factor for vitamin D deficiency is poor absorption of vitamin D, which generally occurs in people with fat malabsorption, given vitamin D is a fat-soluble vitamin. Such fat malabsorption is associated with a variety of medical conditions including some forms of liver disease, cystic fibrosis, and Crohn's disease.

Similarly, people who are obese or who have undergone gastric bypass surgery may become vitamin D deficient overtime given the

greater amounts of vitamin D gets sequestered in the adipose tissue, and the part of the upper small intestine where vitamin D is absorbed is bypassed in such gastric surgery. Hence, people who are obese may need larger than usual intakes of vitamin D to achieve the required 25(OH)D levels comparable to those of normal weight [11].

Minimal erythral dose

A minimal erythral dose (MED) is the amount of sun exposure required to produce a faint pinkness to the skin [31–32]. Previous estimates suggest that a single MED of simulated sunlight will raise circulating levels of 25(OH)D comparable to the ingestion of 10,000 to 25,000 IU of vitamin D₃ [33]. Thus, it is suggested that exposure of the face, arms, hands, and legs for 20% to 25% of that time (i.e., 6 to 8 minutes) 2 to 3 times a week is adequate to meet the body's requirement [34]. This time will vary depending on a number of external and individual factors such as latitude, season, time of day, amount of the clouds [35], age and especially the skin type, as people with dark skin require considerably longer (3–4 times) exposure time [36,37]. Hence, some believe that it is impractical to prescribe a uniform message to the general population given the number of variables that need to be taken into consideration [38].

Season and latitude

Seasonal and latitudinal variations of 25 hydroxyvitamin D levels have long been described, with the highest levels reported during summer sun exposure and decreased levels in late winter season [39]. The likely explanation is that during winter season, more ultra violet B photons are absorbed by ozone layer, due to the fact that sunrays enter at more oblique angle. It has been noted that above the latitude of 37°, there are even more marked decreases in the number of ultraviolet B photons reaching the earth surface during the winter months of November to February. Therefore, very little vitamin D₃ is produced in the skin during the winter [32]. Not surprisingly, Webb et al. have already shown that in the USA, ineffective vitamin D synthesis extended from October through March in Edmonton, where latitude is 52 degree north [40]. Similarly, in Boston (42°N) no vitamin D is produced from November through February [34]. Between 0 and 10 degrees latitude, there is very intense sunlight for several hours before and after noon, year-round. People with pale or untanned skin will have plenty of exposure in just a few minutes. Between 10 and 30 degrees latitude, there are several hours of very strong sunlight each day, especially during the summer, but the hours after dawn and before dusk can be milder. Between 30 and 50 degrees latitude, sunlight can be strong during the summer only, and spring is generally mild. Upwards of 50 degrees latitude, inhabitants are particularly at risk given the summers are often short and they often have pale skin. Dark skin people living at these latitudes are at a very high risk of vitamin D deficiency.

A recent systematic review has evaluated the effect of UV exposure on serum 25(OH)D concentrations by reviewing 8 randomised controlled trials, where four trials used solar exposure and the other four used artificial UV-B sources. [41–48]. This has concluded that 25 (OH)D levels increase with both solar and artificial UV-B exposure [17].

The role of sunscreens

It is important to recognize that sunscreens, while protecting from skin cancers, absorb the ultraviolet radiations before entering the skin and, hence, may block the most important source of vitamin D production leading to a theoretical risk of vitamin D deficient states.

Sunscreens give different level of protection against sunburn, ranging from sun protection factor (SPF) of 6 to >50. Sunscreen controversy about vitamin D deficiency vs. the risk of skin cancer continues to persist. Earlier studies showed a significant drop in the cutaneous production of vitamin D with the use of sunscreens [49-51]. While, it has been shown that a sun protection factor of 8 can reduce the skin production of vitamin D by 95% [49], there are no randomized controlled trials to confirm the same. On the other hand, many trials, including a randomized controlled trial, have revealed that sunscreens do not prevent the production of sufficient vitamin D [43,52-56]. A recent review on this topic has concluded that although sunscreens can significantly reduce the production of vitamin D, their normal usage does not generally result in vitamin D insufficiency [57]. Non-melanoma skin cancers occur on the most sun exposed areas, such as the face and hands, whereas most melanomas occur on the areas least exposed to the sun [58]. Non-melanoma skin cancer is now the UK's commonest malignancy, and malignant melanoma is the commonest cancer in the 15-34 year group [59]. To add to the confusion, apart from the well known benefits of sun avoidance in reducing skin cancers, intermittent and occupational sun exposure has been found to reduce the risk of malignant melanoma [60,61].

Too much sun is the main risk factor for skin cancer; on the other hand, too little sun and wearing sunscreen continuously may lead to vitamin D deficiency [32]. Hence, the health promotion message of emphasizing the importance of UV protection against skin cancers and the issue of low vitamin D due to sunlight avoidance should not be taken as opposing each other. We recommend the sensible exposure to sunlight, for example, a brief exposure to the sun before applying the sunblock.

Infants

Breast fed infants are among the many common groups which are considered at higher risk of developing vitamin D deficiency. Human milk generally provides <25 IU/L to 78 IU/L, which is not enough to meet vitamin D requirements [62,63]. Vitamin D content of breast milk is related to mother's vitamin D status; in other words, vitamin D deficiency in a pregnant woman causes deficiency in the fetus [63]. This can have direct impact on the baby's health, not only during their early life but also as an adult. For example, bone mineral accrual in early childhood and the risk of recurrent wheezing episodes in children have been linked to low vitamin D intake by women during pregnancy [64,65]. Maternal deficiency can cause tetany in neonates, which is caused by hypocalcemia and may accompany infantile or adult vitamin D deficiency. Tetany may cause paresthesias, carpopedal and facial spasm; and, if very severe, seizures. A recent report from Canada has shown that 94% of infants diagnosed with rickets had been breast fed [66]. Hence, American Association of Pediatrics recommends that infants, who are exclusively or partially breastfed, should be supplemented with 400 IU of vitamin D per day [63].

Issues in Defining Vitamin D Deficiency

25(OH) vitamin D is the major circulating form of vitamin D. In clinical practice, measurement of 25(OH) vitamin D is used to diagnose intestinal malabsorption, vitamin D deficiency or intoxication, and to monitor therapeutic response in patients being treated for vitamin D-related disorders. Consensus has not been reached on exact cut-off points of 25(OH) vitamin D levels that can delineate vitamin D deficiency, but most studies and especially Institute of Medicine (IOM) agree on the following cut-offs: levels of <20-25 nmol/l or <12 ng/ml represent vitamin D deficiency that inevitably results in osteomalacia,

if untreated; levels of 25-50 nmol/l or 12-20 ng/ml represent a milder form, often termed insufficiency, which can potentially lead to hyperparathyroidism, accelerated bone turnover and osteoporosis [78]. However, a growing number of researchers warn that the distinction between deficiency and insufficiency is artificial and there is much overlap between the two conditions. Studies have shown a significant improvement in calcium absorption at serum 25OHD level of 67.5 nmol/L compared to 55.5 nmol/L [67]. Similarly, it has been observed that by increasing 25 (OH) vitamin D levels from an average of 50 to 86 nmol/L increases calcium absorption by 45% to 65%, implying that there is significant decrease in intestinal calcium absorption when the level is even 75 nmol/L or less [68]. In contrast to the findings of this study, dropping serum 25OHD from 122 to 74 nmol/L did not produce a significant difference in calcium absorption [69]. This suggests that vitamin D levels should ideally exceed 75 nmol/L, and levels between 50 to 75 nmol/L can be considered relative insufficiency. As new data becomes available, the threshold for diagnosis of vitamin D deficiency is likely to rise even higher. Different values of 25(OH)D have been used as cut-offs to define low vitamin D states, and this depends on the distinct health outcome studied. The most commonly used functional measures to assess the adequacy of vitamin D status include: the level of 25(OH) vitamin D needed to maximally suppress the circulating parathyroid hormone; and the level associated with highest bone mineral density, greatest calcium absorption, reduced rates of bone loss, and reduced fracture rates. In this regard, for a long time the levels of 50nmol/L were considered the cut-offs, given its association with suppression of parathyroid hormone [70]. However, the research has revealed few important facts: serum levels of 25-hydroxyvitamin D are directly related to bone mineral density, and maximum bone density is achieved when the 25-hydroxyvitamin D level reached 100 nmol/L or more; when the level is 75 nmol/L or less, there is a significant decrease in intestinal calcium absorption; similarly, when the level is 50 nmol/L, calcium absorption drops by 35% [68,71]. This stimulates an interesting proposal that cut-offs should be based on determining an optimal level for health as opposed to the minimum level to prevent severe deficiency. Based on this concept, a number of world experts now believe that hypovitaminosis D (i.e. vitamin D 'deficiency') should be defined as a 25-hydroxy (25-OH) vitamin D level \leq 75 nmol/L (i.e., \leq 30 ng/ml in the U.S.) [72]. However, there are some experts who believe this may be too low and they believe the vitamin D sufficiency should be defined as a plasma 25(OH)D concentration of >80 nmol/L [73] and >100 nmol/L [74]. Interestingly, IOM adopts a much conservative approach in defining vitamin D deficiency – serum 25(OH)D was considered as adequate at a level of 20 ng/ml. This report has been discussed in detail somewhere else in this paper.

One major issue contributing to heterogeneous results and limiting the pooling of data is the actual method of measurement of vitamin D, where considerable variability exists. Among the several methods available are the ones based on competitive protein binding assay (CPBA), radioimmunoassay (RIA), enzyme-linked immunoassay, random access automated assay using chemiluminescence technology, high performance liquid chromatography (HPLC) and liquid chromatography-mass spectrometry (LC-MS) [75]. These methods have been shown to give discordant results [76]. For example, the chemiluminescent assay usually provides higher 25(OH) vitamin D results compared to other methodologies. In addition, some can underestimate the total 25(OH)D due to their inability in individually quantifying ergocalciferol [25(OH)D₂] and cholecalciferol [25(OH)D₃] [77]. To overcome these issues, a standard reference preparations

were long awaited so that serum 25(OH)D can be accurately and reliably measured, and validated. In July 2009, a standard reference material has been produced by the National Institute of Standards and Technology (NIST), in collaboration with the National Institutes of Health's Office of Dietary Supplements, and this is hoped to improve the standardisation of operating procedures and reference intervals [78,79].

Prevalence of Vitamin D Deficiency

The prevalence of vitamin D deficiency is very well documented across the globe, and no age, race or the disease spectrum seem to be free of this deficiency. The majority of such studies are focussed on high-risk patients, for example, elderly patients living in institutions, children and young adults, and pregnant females. People in the younger age groups, who are otherwise healthy, are assumed not to require a dietary source of vitamin D. There is accumulating evidence of the high prevalence of vitamin D deficiency in healthy young adults. Among rheumatology outpatient attendees (the patient's ages ranged from 19-91 years of age, the mean age was 53 ± 16 years), a recent study has shown that the age of patients did not substantially influence the prevalence of vitamin D deficiency, as 78% of patients who were aged ≤ 30 years were low in vitamin D [80]. A UK study, which was carried out in similar rheumatology outpatient settings, has shown that vitamin D deficiency is significantly more prevalent amongst general rheumatology outpatients than osteoporotic or osteopaenic patients, irrespective of whether they were receiving vitamin D supplementation at the time of measurement [81]. Cystic fibrosis patients are well known to suffer from low vitamin D levels due to poor absorption of fat-soluble vitamins, and accordingly there are recommendations of its routine monitoring and supplementations in such patients [82-84]. Research has shown that the level of vitamin D deficiency and secondary hyperparathyroidism among general rheumatology patients is comparable to the patients suffering from cystic fibrosis (87% vs. 90% patients had vitamin D levels <30 ng/ml and 21% vs. 25% patients had secondary hyperparathyroidism, respectively [80]. This makes one to suggest that rheumatology patients are at a higher risk of suffering from vitamin D deficiency; however, more research is needed to prove this hypothesis

The likely explanation for vitamin D deficiency in young adults is the low consumption of vitamin D containing foods, lack of exposure to sunlight and limited outdoor activities. The fact that there are very few foods, which are fortified with vitamin D in Europe, complicates this issue. The problem is not confined to the residents of temperate climates; there are also reports of a high prevalence of low vitamin D status among people living in Qatar, Middle East, India, Pakistan, and Ethiopia [85-89]. Moreover, it is alarming to note that in recent years, a resurgence of rickets has been observed among ethnic and cultural minority groups in the United Kingdom, Netherlands, Denmark and in Australasia [90-97]. Similarly, another report, where 25-hydroxyvitamin D were assessed in 8532 European postmenopausal women with osteoporosis or osteopenia, has shown a high prevalence of vitamin D inadequacy in European postmeno-pausal women (79.6% and 32.1% when considering cut-offs of 80 and 50 nmol/L, respectively) [98]. Among HIV-infected patients, a recent study has reported a high prevalence of low vitamin D levels (70%). It has also been observed that some HIV therapies effect vitamin D metabolism and contribute to its deficiency [99]. Very low levels of vitamin D have been described in critically ill patients. Australian researchers have noted that almost half of people in an intensive care unit (ICU) were deficient in vitamin D, with the lowest levels of vitamin D noted among those who were

the sickest or who died during their ICU stay [100]. Similarly, very low levels of vitamin D are reported in almost all different clinical settings, for example, in outpatient clinics, inpatients, and also in primary care settings [101-107]. Clearly, the risk of developing vitamin D deficiency extends well beyond the traditional risk categories of nursing home or older housebound residents.

Treatment of Vitamin D Deficiency

Natural foods are very poor reservoirs of vitamin D, and their fortification is generally not sufficient. The treatment options to achieve optimal circulating level of 25(OH)D are sunlight, artificial ultraviolet light and vitamin D supplementation.

Vitamin D3 vs. Vitamin D2

Vitamin D is available in two different formulations: vitamin D2, better known as ergocalciferol; and Vitamin D 3, also called cholecalciferol. Most experts believe that vitamin D3 is more efficacious than vitamin D2 in raising serum 25(OH) vitamin D levels. Rather, the differential efficacy of vitamin D2 and D3 in the treatment of rickets has been reported since 1930 [108]. There are a multitude of reasons to explain this. For example, vitamin D2 has a shorter half life and an increased rate of clearance from the circulation. There is possibly a higher affinity of hepatic 25-hydroxylase for vitamin D3 than for vitamin D2 [109], and $1,24(\text{OH})_2$ D2 has less affinity for vitamin D receptor than does $1,24(\text{OH})_2$ D3 [110]. This has been confirmed in birds, monkeys and rats [111-113]. In humans, vitamin D3 supplementation has been shown to raise 25(OH) vitamin D levels more than vitamin D2 supplementation. Using equal molar doses of vitamin D2 and D3, a study has shown a much greater increase of 25(OH) D levels with vitamin D3 [114]. Similarly another study reported that to obtain the same effect, the dose of vitamin D2 was 2.5 times the dose of vitamin D3 [115]. In another study, a single dose of 50,000 IU of vitamin D2 or D3 revealed that serum 25(OH)D returned to baseline levels by day 14 with vitamin D2; however, with vitamin D3, the serum 25(OH)D levels peaked at day 14 and remained above the baseline levels up to day 28 [116]. In intervention trials, the average increment in serum 25(OH) D has been estimated at 1.2 nmol/l for every mcg (40 IU) of vitamin D3 [117], and a much smaller increment of only 0.3nmol/L for every microgram of vitamin D2 supplementation [118]. Another very recent trial, using vitamin D doses of 50,000 IU/week for 12 weeks, has revealed that D3 was not only about 87% more potent in raising and maintaining serum 25(OH)D concentrations, but also produced 2- to 3-fold greater storage of vitamin D than does equal doses of D2 [119]. Conversely, it has been shown in some studies that vitamin D2 and vitamin D3 are equally effective in humans to raise circulating 25(OH)D levels [120-122]. We believe that vitamin D3 is a more potent form of vitamin D compared to vitamin D2, and should preferable be used. However, it is important to emphasise that the increase in serum vitamin D levels is inversely related to the starting level of 25(OH)D [123].

Available guidelines

There are a number of recommendations from different clinical organisations for addressing the epidemic of vitamin D deficiency. These clinical practice guidelines are based on expert opinions and a review of the available evidence.

- A position statement from the working group of the Australian and New Zealand Bone and Mineral Society, Endocrine Society of Australia and Osteoporosis Australia outline the people at risk of developing

vitamin D deficiency, and the recommendations for managing vitamin D deficiency [124]. This states that a significant number of people residing in Australia are deficient in vitamin D. The general population should ensure the exposure of hands, face and arms to one-third of a minimal erythral dose of sunlight, or should take vitamin D supplement of 400 IU/day. Patients with vitamin D deficiency should take supplementation of 3000–5000 IU ergocalciferol per day for 6–12 weeks, and in those with moderate to severe deficiency, larger-dose preparations of vitamin D should be considered.

- An international public health project was initiated and named as Daction in an attempt to better address vitamin D deficiency [125]. This particularly emphasises the importance of maintaining vitamin D levels at 100–150nmol/L, and this was considered as safe.

- In 2007, the Canadian cancer society announced recommendations of vitamin D supplementations, based on the mounting evidence linking vitamin D to reduced risk of different cancers [126]. It was suggested that during the autumn and the winter, all adult Canadians should consider taking 1000 IU/day of vitamin D, however, people at high-risk of developing vitamin D deficiency should consider supplementing 1000 IU/day of vitamin D throughout the year.

We believe that a word of caution is needed, given the lack of well-designed randomised-controlled trials to prove or disprove the notion of a causal role of vitamin D in cancer prevention. However, since there is very low risk of harm in enhancing vitamin D levels, we strongly support the need for vitamin D repletion

- Guidelines from Poland also recommend that those adults with inadequate sun exposure or those aged >65 years, require a minimum supplementation of 800–1000 IU/day of vitamin D [127].

- A round table discussion at the 5th International Symposium on the Nutritional Aspects of Osteoporosis was held in 2003, and the consensus among the experts was that a daily intake of 600 IU of vitamin D is required to reach a mean serum 25(OH)D level of 50 nmol/L, and an intake of at least 800–1,000 IU is needed to attain a mean level of 75 nmol/L. Moreover, it was suggested that a level between 50–80 nmol/L is required for optimal bone health, with a consensus median threshold of 75 nmol/L [128].

- International Osteoporosis Foundation (IOF) published its position statement on optimal vitamin D status in early 2010 [129]. These guidelines were specifically designed for elderly women and men aged over the age of 60 to 65 years, since most of the available evidence is based on this particular subset of population. These recommendations are:

- The dose of vitamin D required for optimal vitamin D status depends on an individual's baseline level of 25(OH) D, their BMI, and their level of sun exposure.

- For fall and fracture prevention, a serum 25(OH) D threshold of 75 nmol/L is considered optimal.

- Serum 25(OH)D increases by about 1 ng/mL (2.5 nmol/L) for every 100 IU of additional vitamin D each day

- The estimated average vitamin D requirement to acquire the serum level of 75 nmol/L is 800 to 1,000 IU per day. This might need to be adjusted depending on the associated risk factors, such as, the starting level of 25(OH)D, obesity, associated osteoporosis, poor sun exposure, malabsorption and residents or immigrants from South Asia and Middle East.

- To measure serum vitamin D levels for such at risk populations, as this not only helps to estimate the repletion dose, but also serves as a baseline for future retesting.

- Osteoporosis Canada published its guidelines statement in

September 2010 [130], and supported recommendations aiming for serum 25-hydroxyvitamin D levels above 75 nmol/L. These recommendations were directed for general population and not confined to osteoporotic population. Vitamin D supplementation was considered indicated given that most Canadian adults have insufficient exposure to sunlight and dietary intake to maintain this level throughout the year. Recommended intake for low-risk and younger adults was suggested at 400–1000 IU daily and for high-risk and older adults, to 800–2000 IU daily.

- In late 2010, new Canadian guidelines for the management of *osteoporosis* were published, which recommend higher intakes, with routine supplementation at 400 to 1000 IU daily for those at low risk and up to 2000 IU daily for high-risk individuals [131]. It is important to note here that such higher intake of vitamin D are suggested for osteoporotic patients only.

- In November 2010, Institute of Medicine (IOM) updated their original 1997 set of recommendations. They concluded that the majority of Americans and Canadians are receiving adequate amounts of both calcium and vitamin D, and also warned regarding the toxicity of vitamin D with bigger doses [78]. Although, they reviewed a range of health outcome measures, inconclusive and unreliable evidence of vitamin D and calcium supplementation was noted in all of these outcomes, apart from its role in bone health. Therefore, these recommendations are based on the role of vitamin D and calcium in bone health only. These recommendations suggest: the adequate level of serum 25(OH)D is 45nmol/L (20 ng/ml), with a range of 45–75 nmol/L (20–50 ng/ml); there is no improvement in bone growth and maintenance with vitamin D levels above 75 nmol/L (50 ng/ml); the upper limit of daily intake is now doubled to 4,000 IU of D3 per day; and recommended dietary allowance (RDA) has been set at 600 IU/day for everyone apart from those aged >70 years of age, where RDA was suggested to be at 800 IU/day. It should be emphasised that IOM was given the task of assessing the current data on health outcomes associated with calcium and vitamin D, and to update dietary reference intakes. Hence, this IOM report is a guide to food manufactures, and it was not the mission of that report to offer medical guidance for physicians, rather this should be left to the various societies issuing their own medical recommendations. These recommendations have been controversial [132], but one good outcome is the undoubted recognition of the key role of calcium and vitamin D in skeletal health, consistent with a cause-and-effect relationship. Hence, rheumatologists should routinely consider identifying and treating this extremely common condition – low vitamin D state - which has got excellent potential for both prevention and treatment.

Effects of intermittent high-dose of vitamin D regimens

It is also important to discuss recent concerns regarding very high doses of vitamin D regimens. A double blind placebo-controlled trial has shown that a single annual 500 000-IU oral dose of cholecalciferol (vitamin D3) increased risk of falls and fractures, with the greatest increase occurring during the first 3 months after dosing [133]. Similarly, another randomized, double-blind, placebo-controlled trial has evaluated the efficacy of annual 300,000 IU intramuscular vitamin D2 (ergocalciferol) injection over 3 years. This particular study has reported that annual high doses of vitamin D were ineffective in preventing non-vertebral fractures [134]. It seems that rather than very high doses of intermittent vitamin D replacements, more frequent lower-doses regimens should be opted. Clearly, further research is needed to better understand these findings.

Controversy over Calcium and Vitamin D: Calcium or No Calcium

An acceptable threshold for calcium intake has not been defined so far. Most studies have used a daily calcium dose of 1,000-1,200 mg [135-138]. There had been some controversy as regards the additional benefit of adding calcium to vitamin D for fracture prevention. The arguments against achieving any significant benefit of adding calcium to vitamin D comes from two studies, which showed that non-vertebral fracture prevention is calcium-independent provided the vitamin D dose is greater than 400 IU per day [139,140]. Moreover, a 2007 meta-analysis has revealed that calcium supplementation, whether in lower or higher doses, had no effect on hip fracture risk reduction [141]. Likewise, a 2009 meta-analysis revealed no additional benefit of adding calcium therapy to higher doses of vitamin D supplementation (482-770 IU/day) for non-vertebral fracture risk reduction [142]. On the contrary, Tang et al. has shown in 2007, through an extensive meta-analysis, that combination of calcium and vitamin D is more effective than calcium or vitamin D alone. More importantly, it showed that most papers reporting a negative effect of the calcium-vitamin D association were linked to a poor adherence to treatment [143], and minimum doses of 1200 mg of calcium and 800 IU of vitamin D were recommended for best therapeutic effect.

Similarly, three recent systematic reviews, including a Cochrane review, have concluded that vitamin D supplementation without additional calcium intake was ineffective in preventing fractures [144-146]. A consensus statement from leading osteoporosis societies has suggested the combination of vitamin D with calcium, both for their better efficacy and, perhaps, for optimising adherence [147].

Extraskelatal adverse events of calcium intake are quite complicated. Recent meta-analysis of randomised placebo controlled trials showed that calcium supplementation at doses of ≥ 500 mg/day without additional vitamin D was associated with a 30% increase in the incidence of myocardial infarction and an insignificant increase in the risk of stroke and mortality [148]. Similarly, a 2008 randomised controlled trial of 1,000 mg/day of calcium revealed a 47% increase in relative risk of combined cardiovascular endpoints [149]. Furthermore, the association of calcium intake with renal stones is well established. A randomized controlled trial in 36,282 postmenopausal women reported that a combination of supplemental calcium (1,000 mg/day) and vitamin D (400 IU/day) was associated with a 17% increase in the incidence of renal stones or renal insufficiency [138]. On the contrary, a recent analysis of calcium supplementation and the risk of atherosclerotic vascular disease in older women has shown calcium supplementation of 1200 mg daily does not significantly increase the risk of atherosclerotic vascular disease in elderly women. This analysis was based on the results of a 5-year randomized controlled trial with a further 4.5-year follow-up observation [150]. Similarly, long-term follow up of RECORD study patients has shown that daily vitamin D or calcium supplementation did not affect vascular disease mortality [151]. Studies to date do not permit definitive conclusions since no randomised controlled trials have been conducted primarily to assess the effect of calcium supplementation on vascular events. Rather the information is based on secondary analysis and reviewing the unpublished data on cardiovascular events from the previous studies. Due to these concerns, it seems reasonable to recommend supplementing vitamin D and calcium only to those who are at increased risk of osteoporosis, and very reassuringly, calcium and vitamin D supplementation does not influence coronary or cerebrovascular risk in generally healthy postmenopausal women [146,152]. We recommend that at the very least

all post-menopausal women and men over 65 years take daily calcium supplementation of 1200 mg/day, and it is imperative to assess dietary calcium consumption and adjust the total calcium intake accordingly. This is worth highlighting that presumed normal range of calcium levels differ in many countries, and it is vital to use reference local population otherwise, there is a potential risk of labelling erroneously hypercalcaemia/hypocalcaemia. Clearly, further work needs to be done.

Safety of Repleting Vitamin D Stores

Vitamin D therapy is generally considered safe in most individuals. There is no evidence of adverse effects with serum $25(\text{OH})\text{D} \leq 70$ ng/ml, i.e. 175 nmol/L. In addition, published reports of vitamin D toxicity have nearly all involved intake $\geq 40,000$ -50,000 IU per day for prolonged period of times [153]. It has been shown that healthy humans produce about 4,000 units of vitamin D a day, from all sources [154]. Moreover, studies using 10,000 IU of vitamin D/day for up to 5 months did not cause toxicity [155]. Currently, the upper tolerable level for vitamin D supplementation is 2,000 IU/day for both males and females (1 year and older) including pregnant and nursing females, and 1,000 IU for infants (0-12 months). Some experts raise the upper limit of vitamin D supplementation to 10,000 IU as per many safety trials [156]. The issue of toxicity was especially highlighted when accidental overfortification of milk from 1985 to 1991 led to a suspected outbreak of hypervitaminosis D associated with severe illness and death in the USA [157]. It is unfortunate that most trials have excluded subjects with renal insufficiency or hypercalcemia, and included short durations of exposure to vitamin D. The WHI trial was the largest trial (seven years follow up of 36,282 subjects) showing a significant increase in kidney stones among postmenopausal women taking only 400 IU vitamin D3 plus calcium 1,000 mg a day [138]. However, it is difficult to make firm conclusions from this study due to the following: documentation was made of only patient reported renal stones rather than the review of medical records or confirmed by physicians, and very poor compliance rate of only 50-55%. A systematic review has found inadequate reporting quality of vitamin D toxicity and inadequate power to detect adverse events in most of the reported trials; however, good tolerability of vitamin D supplementation above current reference intakes was observed [17].

One plausible explanation for vitamin D toxicity is the combination of heavy sun exposure with excessive supplementation of vitamin D. There are a number of contraindications to vitamin D therapy. Hypersensitivity to vitamin D can occur, and primary hyperparathyroidism is the most common example where vitamin D may exaggerate hypercalcemia. Occasionally, hypercalcemia due to vitamin D therapy can occur when large groups of elderly people are given vitamin D supplements, but this is likely due to the fact that vitamin D deficiency can mask primary hyperparathyroidism in this group. In addition, patients with chronic granulomatous diseases, such as sarcoidosis, tuberculosis and lymphoma can become hypercalcemic with vitamin D supplementation as there is additional production of 1,25-dihydroxyvitamin D from macrophages [158,159]. These conditions are preferably labelled as "vitamin D hypersensitivity syndromes".

Vitamin D toxicity remains undetected for a considerable period of time, and usually presents initially with elevated urine calcium excretion and later on, an elevated serum calcium levels. Early symptoms of hypercalcemia may include nausea, vomiting, and anorexia, followed by polyuria, polydipsia, weakness, fatigue, somnolence, headache, dry mouth, metallic taste, vertigo, tinnitus, and ataxia. Renal impairment and metastatic calcifications may occur, particularly affecting the kidneys. Elevated serum calcium levels are a constant finding when toxic symptoms occur. Serum $25(\text{OH})\text{D}$ levels are usually elevated >150 ng/mL (>375 nmol/L). For the diagnosis of vitamin D toxicity, levels of $1,25(\text{OH})_2\text{D}$ need not to be measured, as they may be normal.

Treatment consists of stopping vitamin D, restricting dietary calcium, restoring intravascular volume deficits, and, if toxicity is severe, giving corticosteroids or bisphosphonates. However, it is quite reassuring that toxicity stemming from pharmacological doses of vitamin D is very uncommon, and majority of such reports of toxicities are caused by accidental overdose. Vigilance is imperative as the response to vitamin D supplementation or sun exposure widely varies; however, there are no consensus regarding how to best monitor those using regular supplementations.

Conclusion

In summary, vitamin D deficiency is now well recognised as a growing health concern. There is enough evidence to support its role in bone health; however, there is insufficient evidence to prove its role beyond musculoskeletal health. Given the extreme rarity of vitamin D toxicity, it seems reasonable to advise general public (at the very least in all post-menopausal women and men >65 years of age) regarding the use of such foods, which contain higher contents of vitamin D, or to use fortified food products. A clear public health strategy and guidance on vitamin D supplementation is warranted. We hope that with growing interest and research in the role of vitamin D, effective management strategies will emerge.

Future Perspective

Firstly, standardization of vitamin D deficiency and repletion protocols are required to better frame future studies of vitamin D supplementation. Secondly, studies should also aim for genotype scoring in addition to the common risk factors for prediction of various health outcomes; in other words to look for most “at-risk” genotype. Thirdly, while a wealth of epidemiological studies support the importance of vitamin D beyond bone health, further trials in the form of well-designed randomised-controlled trials are required before claims can be made about the role of vitamin D in the prevention of chronic diseases.

Summary

- Vitamin D deficiency remains under recognised and untreated
- Vitamin D2 is a plant extract and Vitamin D3 is synthesized by humans in the skin, when it is exposed to ultraviolet-B (UVB) rays from sunlight
- 25-OH vitamin D is the predominant circulating form of vitamin D in the blood and because of its close regulation by the availability of vitamin D, measurement of 25(OH) vitamin D is the most reliable indicator of vitamin D status
- In vitro studies have shown that molecular mechanisms of action of 1,25-dihydroxyvitamin D include genomic and non-genomic effects. Genomic effects of vitamin D are mediated by classical gene transcription or protein synthesis route, and non-genomic effects are mediated by the formation second messengers
- Common factors associated with vitamin D deficiency include poor intake, malabsorption, obesity, season and latitude, sunscreens, increased skin pigmentation, age and especially the skin type
- Consensus has not been reached on exact cut-off points of 25 (OH) vitamin D levels that can delineate vitamin D deficiency, but most studies agree that levels of <20-25 nmol/l or <12 ng/ml represent the severest deficiency that inevitably results in osteomalacia, if untreated
- A growing number of researchers warn that the distinction between deficiency and insufficiency is artificial and there is much overlap between the two conditions.

- The cut-offs to define vitamin D deficiency should ideally be based on determining an optimal level for health as opposed to the minimum level to prevent severe deficiency

- It is hoped that the standardisation of operating procedures and reference intervals will improve with the production of a standard reference material by the National Institute of Standards and Technology (NIST), in collaboration with the National Institutes of Health's Office of Dietary Supplements.

- The prevalence of vitamin D deficiency is very well documented across the globe, and no age, race or the disease spectrum seem to be free of its presence.

- There is some evidence to support that vitamin D3 is more efficacious than vitamin D2 in raising and maintaining serum 25(OH) vitamin D levels

- There is no evidence of adverse effects with serum 25(OH)D \leq 70 ng/ml, i.e. 175 nmol/L. However, most trials have excluded subjects with renal insufficiency or hypercalcemia, and included short durations of exposure to vitamin D. Continuous monitoring is essential as the response to vitamin D supplementation or sun exposure widely varies.

- Varied results of calcium-vitamin D association for bone health have been reported, however, based on the current evidence, we recommend (at the very least in all post-menopausal women and men > 65 years) the combination of minimum doses of 1200 mg of calcium and 800 IU of vitamin D for best therapeutic effect.

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