

Vitamin D3: The Flip Side of a Useful Hormone

Ibraheem M. Gambo^{1*}, Mohammed M. Bello², Nanyak Z. Galam¹, Enyikwola, EO¹

¹Department of Human Physiology, Faculty of Medical Sciences, University of Jos, Nigeria.

²Department of Human Anatomy, Faculty of Medical Sciences, University of Jos, Nigeria.

*Corresponding author: ibroabs@yahoo.com

ABSTRACT

Vitamin D may be regarded as one of the oldest vitamin known to man. It can also be said to have preceded the creation of man as an earthly being. This article tries to expose some of the benefits or otherwise of vitamin D as its popularity in different aspects of human lives- medical, social and physical- is gradually increasing. While a large body of evidence promotes its supplementation and deemed it useful for healthy living, many investigators are wary of its potential toxicity to the body. Clearly, there is a need for a widely accepted guidelines relating to its supplementation, cut off values, relevant biomarkers and a reliable prevalence data of its insufficiency.

Key words; Vitamin D, supplementation, toxicity.

1. INTRODUCTION

Vitamin D is a group of fat-soluble prohormones, the two major forms of which are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D is obtained from sun exposure, food, and supplements. Human skin is rich with latent pre-vitamin D, which is activated by sunlight. Humans usually obtain vitamin D through sunlight exposure. The skin provides the major source of vitamin D where 90-95 percent of vitamin D requirement comes from photosynthesis in the skin. Despite the Vitamin D found in foods, many people fail to obtain even the modest 'adequate' intake every day. People who do not spend much time in the sun and other people at high risk for vitamin D deficiency include: the elderly, who convert less vitamin D with sunlight exposure, compared to younger people; the obese; and dark-skinned individuals, due to high melanin skin content. Oral intake of vitamin D has therefore become necessary, as humans developed lifestyles involving less and less sun exposure. A growing body of research indicates that vitamin D deficiency contributes to a broad spectrum of conditions such as high blood pressure, poor insulin sensitivity, inflammation, and other fundamental processes that underlie heart disease.

2. HISTORICAL GLIMPSE

Hippocrates, the father of medicine, was reported to have used heliotherapy or exposure to sunlight to treat phthisis. The first scientific description of a vitamin D-deficiency, namely rickets, was provided in the 17th century by both Dr. Daniel Whistler (1645) and Professor Francis Glisson (1650). It was only at the beginning of the twentieth century that supplementation with cod liver oil (a rich dietary source of vitamin D3) and later sun exposure were used to cure rickets and osteomalacia. In 1821, Sir Edward Mellanby reached the conclusion that the action of fats in rickets is due to a vitamin or accessory food factor which they contain, probably identical with the fat-soluble vitamin (<http://historyofsciences.blogspot.com>). This opened the door for further investigations that resulted in the discovery of vitamin D. The first analogue of the vitamins D was determined in the 1930s in the laboratory of Professor A. Windaus at the University of Gottingen in Germany (<http://historyofsciences.blogspot.com>).

As humans moved from UVB rich equatorial areas to more northern areas, natural selection favoured steadily lighter skins, so that less and less UVB was necessary to synthesise the vitamin D required for optimal skeleton robustness and muscle functioning (Loomis, 1967). Landmark works by Jablonski and Chaplin (2000) have shown that skin reflectance is strongly correlated with absolute latitude and UV radiation levels, suggesting that the main role of melanin pigmentation in humans is the regulation of the effects of UV radiation on the contents of blood vessels located in the dermis. This regulation is deemed to protect against the UV induced degradation of folic acid, a member of the vitamin B family that is essential for numerous vital metabolic and reproductive functions. Folic acid has, among other functions, involvement in the development of the neural tube, spermatogenesis, and DNA

replication. Evolutionary pressure led to the lightening of skin of *Homo sapiens* migrating further away from the equator that represents a compromise solution to the conflicting physiological requirements of photo protection for folic acid preservation and endogenous UVB induced vitamin D₃ synthesis.

Female skin is generally lighter than that of the male, and this may be required to permit synthesis of the relatively higher amounts of vitamin D₃ necessary during pregnancy and lactation.

2.1 Cutaneous synthesis of vitamin D

Endogenous synthesis of vitamin D₃ consists of a UVB-induced photochemical reaction resulting in the formation of previtamin D₃ from the provitamin D₃ 7-dehydrocholesterol (7-DHC) in basal and suprabasal layers of the skin. 7-DHC is formed in the skin from cholesterol thanks to the $\Delta 7$ -reductase present in the epidermal keratinocytes (Bonjour et al.,1987).

Approximately 65% of 7- DHC per unit area is found in the epidermis; the remaining 35% is in the dermis. The 5,7-diene of 7-DHC absorbs UVB radiation causing it to isomerise, resulting in a bond cleavage between carbon 9 and 10 to form a 9,10-seco-sterol, the previtamin D₃. The action spectrum for previtamin D₃ production spans between 260 and 315 nm (CIE, 2006).. Maximum spectral effectiveness ranges from 297 to 303 nm. The effectiveness of UVB on the formation of previtamin D₃ in the skin is influenced by several factors including UVB absorbing molecules like melanin, DNA, RNA, proteins, and 7-DHC skin content. Previtamin D₃ then undergoes nonenzymatic isomerisation to form vitamin D₃ and this process is temperature-dependent, i.e., the higher the temperature, the larger the amount of previtamin D₃ that isomerises into vitamin D₃. The vitamin D₃ formed in the skin is then swept out into the blood stream by the Vitamin D Binding protein (DBP), and α -globulin that has a high affinity to vitamin D and its metabolites. The constant extraction of vitamin D from the skin by DBP avoids the local accumulation of vitamin D₃ and allows perpetuation of the isomerisation of previtamin D₃ into vitamin D₃. UVB-triggered conversion of 7-DHC to previtamin D₃ is a rapid reaction which needs only a few seconds. In contrast, the half life ($\tau_{1/2}$) of the isomerisation of previtamin D₃ to vitamin D₃ in human skin is approximately 2.5 hours (Tian et al.,1993). The circulating concentrations of vitamin D₃ are at their maximum levels within 12-24 hours after UVB exposure (Chen et al.,2007b; Adams et al.,1982). The quantities of vitamin D₃ synthesised by the skin are very small compared with the concentration of the precursor 7-DHC (assumed $\approx 2,000$ ng/cm²). Human skin subjected to ultraviolet radiation in vivo produces about 25 ng vitamin D₃ per cm² according to a conversion rate of 7-DHC to vitamin D₃ of 1.3% (Davie and Lawson, 1980). The ultraviolet spectrum irradiating the skin modulates the respective proportions of previtamin D₃ photosynthesis and its photo-isomerisation in vitamin D₃, lumisterol, and tachysterol (MacLaughlin et al.,1982).

In this respect, quantities of vitamin D₃ synthesised in the skin may be different if say, artificial sources of UV are used instead of natural sunlight.

2.2 Should we supplement our diet?

A body of evidence shows vitamin D as a promising candidate that may influence many clinical disorders. scientists published impressive new evidence that vitamin D is involved in a staggering array of diseases: age related cognitive decline, heart disease, breast cancer, tuberculosis, Parkinson's disease, prostate cancer, chronic pain, fractured hips, premenstrual syndrome and diabetes (John Cannell at <http://cholecalciferol-council.com>)

Accumulating epidemiologic and clinical intervention trial data suggest that increased vitamin D status may decrease the risk of cancer, especially that related to colorectal adenomas (Giovannucci,2006; Giovannucci et al, 2006; Grau,2003; Holt et al, 2006). Other evidence suggests that increased vitamin D status may help maintain physical strength in the elderly (Kenny et al,2003) and also be protective against falls (Bischoff et al 2003). Also, improved vitamin D and calcium status may decrease the prevalence of metabolic syndromes, including diabetes mellitus (Liu,et al,2005). Treatment with calcium and vitamin D shows some promise for reducing the bone loss in cystic fibrosis patients(Haworth et al,2004) However, despite its relative usefulness, it is surrounded by many controversies that range from the validity of supplementations to toxicity. While some quota believes that it is relatively harmless with a safer therapeutic index that is perhaps better than water, others hold that it as a potentially toxic substance.

Quaker Oats received the first license in February 1927 to manufacture vitamin D-enriched breakfast cereal. Licenses were issued to pharmaceutical companies to manufacture a medicinal vitamin D product. By 1934, the irradiation

process was extended to produce vitamin D–fortified milk. Soon, vitamin D fortification was achieved inexpensively by adding vitamin D directly to milk(<http://mpkb.org/home/vitamind>)

The fortification of milk with vitamin D was also adopted in Europe; however, the process was not closely monitored, and in Great Britain it caused an outbreak of vitamin D intoxication, or hypercalcemia. This outbreak led to the banning of the vitamin D fortification of milk in most of Europe (Rajakumar et al,2007).

As a result of this potential toxicity, various national committees in the 1950s and 1960s have recommended the discontinuation of fortifying food with vitamin D. An attempt should be made to restrict the intake from all sources save from the production of the skin. Efforts should particularly be made to dispel the concept of vitamin D preparations as tonics, and consideration should be given to the ease with which vitamin D preparations can be acquired through commercial sale (Linden,1974).

Since the turn of the new century, vitamin D supplementation had seen a renewed interest. From men that requires the re-growth of their balding hair to those that need improvement in their virility; from weight reduction to improvement in athletic performance; from the management of chronic pains to cancer prevention. A September 2010 report published by *Nutrition Business Journal* points out that in the previous two years, vitamin D supplement sales to consumers have increased by more than 100% per year – a four-fold increase(Heaney and Holick,2011). It is reported that rickets is making a resurgence in African American young children who receive their total nutrition from breast feeding (Kreiter et al., 2000). Thus, supplementation is likely to become inevitable in this group.

Some authorities strictly depart from the basis for vitamin D supplementation. In 2010 Drs. Reddy and Gilchrest ran an editorial indicating that there is no basis for vitamin D supplementation in the general population because neither the biologic validity of “vitamin D insufficiency” nor the health benefit of maintaining high serum 25(OH)D levels has been established for the general population (Gilchrest and Reddy,2010). This view holds that unless there is a body of evidence scientifically confirming vitamin D insufficiency in the population, general supplementation is not required. For individual that are sufficient in this vitamin, the risk for toxicity may be increased.

In the United States, the Food and Nutrition Board(FNB) evaluated the potential for high intakes of vitamin D to produce adverse effects and set a safe Tolerable Upper Intake Level (UL) of 50 µg (2000 IU) for vitamin D₃(Food and Nutrition Board,1997) the European Commission Scientific Committee on Food (SCF) also identified a vitamin D₃ UL of 50 µg (Scientific Committee on food,2002)

Apparently, the current approach to vitamin D supplementation does not take into account the random variation that may be inherent to different subjects. If the optimal serum 25(OH)D level for skeletal health is 30 ng/mL or greater, then vitamin D insufficiency is widespread, affecting about 75% of adults based on a recent survey of more than 20,000 Americans. However, after a comprehensive analysis of existing research studies, the Institute of Medicine recently concluded that nearly all individuals are vitamin D replete when their 25(OH)D levels are 20 ng/mL or greater (Hansen,2011). Furthermore, two recent publications challenge the belief that 25(OH)D levels greater than 30 ng/mL are optimal for bone health. In a randomized, placebo-controlled trial, high-dose, once- yearly vitamin D therapy increased the incidence of fractures and falls. The second study reported that high- dose vitamin D did not reduce levels of parathyroid hormone or bone resorption among adults with 25(OH)D levels less than 32 ng/mL at baseline. It is time to question whether serum 25(OH)D levels of 30 ng/mL or greater are necessary for all individuals(Hansen,2011). In Europe, fortification with vitamin D varies. In some countries, the level of fortification can be quite low, at least in comparison to other developed countries (Hypponen et al,2004).

Calcidiol(25-hydroxy-vitamin D) is usually the form in which vitamin is stored. It has a half-life of 20-29days and has a large volume of distribution. The serum levels of this form are useful in the diagnosis of vitamin D overdose during which the serum levels of the bioactive form may be normal. . In healthy individuals, calcidiol levels are normally between 32 to 70 ng/mL (80 to 175 nmol/L), but these levels may be as much as 15-fold greater in cases of vitamin D toxicity (http://www.news-medical.net/health/what_are_hormones.aspx)

Certain review suggested that there is little prospect of exposure of the healthy general population to toxic levels of vitamin D with current levels in fortified foods and dietary supplements. Therefore, total exposure to vitamin D, including autogenous production under UV light stimulation, is very unlikely to exceed the proposed tolerable Upper intake Level (UL) value. Combining the proposed UL with total erythemic sunlight exposure and typical dietary and supplemental sources all at once would still result in a serum 25(OH)D concentration (≈500 nmol/L) that is well below

the estimated concentration associated with hypercalcemia (>600 nmol/L). Indeed, there is a lot of room for increased vitamin D intakes without risk of overdose(<http://ajcn.nutrition.org/content/85/1/6/>).

All known cases of vitamin D toxicity with hypercalcemia have involved intake of over 1,000 micrograms/day (40,000 IU) if taken in an attempt to increase the levels of vitamin D. Most officially-recorded historical cases of vitamin D overdose have occurred due to manufacturing and industrial accidents.

Some symptoms of vitamin D toxicity are a result of hypercalcemia (an elevated level of calcium in the blood) caused by increased intestinal calcium absorption. Vitamin D toxicity is known to be a cause of high blood pressure. Gastrointestinal symptoms of vitamin D toxicity can include anorexia, nausea, and vomiting. These symptoms are often followed by polyuria (excessive production of urine), polydipsia (increased thirst), weakness, nervousness, pruritus (itch), and eventually renal failure. Other signals of kidney disease including elevated protein levels in the urine, urinary casts, and a build up of wastes in the blood stream can also develop. Another study showed elevated risk of ischemic heart disease when 25D was above 89 ng/mL. Vitamin D toxicity is treated by discontinuing vitamin D supplementation, and restricting calcium intake. If the toxicity is severe blood calcium levels can be further reduced with corticosteroids or bisphosphonates. In some cases kidney damage may be irreversible. According to some sources, endogenous production with full body exposure to sunlight is approximately 250 μ g (10,000 IU) per day.

Even in the face of all these, this important vitamin has a rich prospect in re-shaping the understanding of several physiologic processes. Beyond the skin and the kidneys, different tissues of the body are now known to synthesise the vitamin. Although the physiologic function of the extra renal production of 1,25(OH)₂D₃ is not well understood, there is mounting evidence that this synthesis may be important for cellular health and disease.

3. CONCLUSION

Irrespective of the prevailing arguments concerning vitamin D supplementation, the most reliable and readily available source of vitamin D remains the sun. Obviously, there is the urgent need for researchers to reach a consensus using evidence based data on the tolerable upper intake level that may not pose any hazard to health. The future seems bright for this substance that started from a very humble beginning and graduated from being just a vitamin to a hormone with magic bullet potentials. Basic issues that need prompt attention have been highlighted thus far. These include- better definitions of adequate and insufficient, with meaningful cutoff values and biomarkers that have functional relevance. We need sufficient evidence to make practical evidence-based recommendations; determination of biomarkers and functional outcomes for bone and non-bone tissues that might reflect vitamin D status; Better prevalence estimates, domestically and globally. What is suboptimal, compared with frank deficiency?(Mary and Daniel , 2004). While we allow the sun to warm our human spirit, the flip side of vitamin D should be given due attention.

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