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OPINION ARTICLE

Vitamin D

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"Science commits suicide when it adopts a creed"
Thomas Huxley

Vitamin D is a molecule that has been present in living beings since early in evolution.[1] The process by which ultraviolet light activates vitamin D synthesis involves a great variety of metabolic activation and signaling pathways. Vitamin D was linked to bone metabolism early on but has more recently been implicated in a group of metabolic functions beyond the maintenance of bone mass.[2] These functions range from immune regulation to protection against cancer, infection, metabolic syndrome, or chronic pain. The roles of many other vitamins have also been revised recently: vitamin C deficiency has been implicated in the pathogenesis of atherosclerosis, while a deficiency of vitamin E has been seen to impact upon prostate cancer. Some of the surprises in recent redefinitions of the roles vitamins play, alongside the discovery that vitamin D deficiency is common amongst large population groups in the industrialized world,[3] has prompted many studies and much speculation.

Vitamin D is known to be present in primitive organisms such as phytoplankton, explaining why the bluefish that feed on these microorganisms make such fish a major dietary source of the vitamin for humans. As organisms evolved, this molecule came to play an important regulatory role in calcium metabolism and bone mass accumulation. There is even speculation that the extinction of the dinosaurs may have been related to the failure of vitamin D synthesis when a meteorite in what is now the Gulf of Mexico raised a blanket of dust 65 million years ago, preventing sufficient ultraviolet radiation from reaching the Earth's surface.[4] The theory is that species such as dinosaurs, with their enormous bone mass, were unable to maintain calcium metabolism in these circumstances and therefore became extinct. The small mammals that are the ancestors of primates were able to survive the adverse circumstances, however, because they were nocturnal, had lower bone masses, and were less dependent on ultraviolet light.[5] As primate brain size increased over time, more complex mechanisms of thermoregulation would become necessary for neuronal function and hominins would begin to lose hair, acquire more sweat glands, which would also become more active. They would also require darker skin to protect them from damaging ultraviolet radiation. These theories neatly explain why the most highly evolved primates had dark skin—a trait that also provided the skin with protection against light-activated degradation of folic acid,[5,6] which is essential for reproduction and perpetuation of the species as it plays an active role in the prevention of neural tube defects.

However, dark skin is also less able to synthesize vitamin D, introducing a drawback, but one that would pose few problems for the early humans who lived in tropical and subtropical environments with very high levels of ultraviolet radiation.

As *Homo sapiens* migrated to more temperate zones, groups that moved nearer to the poles became lighter

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skinned, allowing the human body to maintain vitamin D synthesis in habitats with less ultraviolet radiation. Fair-skin phototypes have also been shown to afford more resistance to cold—a survival advantage in glacial periods.

However, recent human migrations have resulted in large numbers of darker skinned individuals living in temperate zones—African Americans in the United States or Asian Indians in the United Kingdom, for example—a situation that exposes them to the risk of vitamin D deficiency. At the same time, many fair skinned individuals have settled in extremely sunny regions (the example usually given is the white population of Australia), exposing them to a high risk of skin cancer. Some of the latter populations also experience vitamin D deficiency as an outcome of excessive use of photoprotection measures. The fact that vitamin D deficiency is even found in very sunny countries makes us question whether there could be suboptimal ultraviolet exposure among groups with a sedentary lifestyle, living and working in enclosed environments where ultraviolet light is replaced by visible light. Serious cases of rickets associated with extreme vitamin D deficiency were first described in the United Kingdom early in the Industrial Revolution. The change from rural to urban environments and indoor work, as well as poor nutrition, led to a veritable epidemic of bone disease.

Sufficient plasma concentrations of vitamin D can be achieved through ultraviolet-activated production. Dietary contributions are few and a standard Western diet rarely includes the intake of foods such as blue fish that are rich in vitamin D. In fact, the majority of dietary vitamin D now comes from supplements added to milk or margarine. Where the dietary contribution is inadequate—as it usually is—the body is capable of synthesizing the molecule and it would therefore be very logical to replace the term 'vitamin D' with the term 'hormone D.'

A 5- to 20-minute dose of ultraviolet radiation at a level insufficient to cause erythema (the optimum peak for previtamin D synthesis is 296 nm) is estimated to produce 20,000 units. As soon as this level is achieved the ultraviolet radiation begins to degrade any additional vitamin D produced and limit production. Furthermore, the erythema and tanning resulting from repeated exposure also constitute limiting factors. The delayed effect of tanning allows for high initial synthesis of the vitamin that becomes more limited once a sufficient level has been achieved by the body.

While the metabolic pathway leading to vitamin D is extremely well-known, certain concepts deserve repeating. Cholecalciferol is synthesized from 7-dehydrocholesterol in the skin under the action of UV-B light. In the liver, cholecalciferol is transformed into calcidiol, which is transformed into calcitriol, the active form of vitamin D, in the kidneys. Renal calcitriol is preferentially involved in bone metabolism. In recent years, calcitriol synthesis has been described in many other tissues as a non-preferential process that can be affected by degrees of vitamin D deficiency. Extrarenal calcitriol is thought to be implicated in a group of various autocrine, paracrine and recently identified functions, in cancer, and in immune regulation; others are still under investigation. Some suggest that vitamin D deficiency would not cause the same problems as would insufficiency. At serum levels of calcidiol of less than 5 ng/mL, the renal calcitriol pathway will be compromised, with immediate effect on calcium metabolism and possibly secondary hyperparathyroidism, bone resorption, osteomalacia, osteoporosis, or even rickets. At calcidiol levels of 5 to 20 ng/mL, the organism will tend to conserve the renal calcipotriol pathway, but synthesis in other tissues will be compromised, and with depletion the autocrine and paracrine functions of vitamin D will be affected and other changes will take place. Calcidiol levels of between 30 and 35 ng/mL are sufficient to protect all pathways.

The key questions are what levels of calcidiol should be considered sufficient, whether vitamin D levels are adequate in Western populations, whether such levels remain constant throughout the year, what factors influence sufficiency or insufficiency, and whether insufficient levels have any adverse effects. Recent findings go some way toward clarifying the answers, but it is still too early to draw categorical conclusions. In strictly objective terms, we can currently state that up to 50% of the population in the developed world has suboptimal levels of calcidiol in the blood (5-20 ng/mL) in the less sunny months of the year, with a greater risk for darker skinned groups resident in temperate regions, the elderly, women, and individuals who are sedentary or obese. However, insufficiency has also been identified in healthy young people living in temperate and subtropical zones[7,8] (Hawaii, India, Brazil, Arizona, southern Florida, and Australia) and no convincing explanation has so far been proposed for this phenomenon. There is much speculation that the Western lifestyle coupled with sedentary habits, inadequate diet, and suboptimal exposure to ultraviolet light throughout most of the year—where daily, ongoing and gradual exposure has been replaced by recreational exposure at weekends and during holidays—results in risky behavior patterns that trigger skin cancer. Speaking at a meeting in Dundee in 2010, Brian Diffey,[9] Professor of Photobiology at the University of Newcastle, England, concluded that 60% of annual sun exposure for people in the United Kingdom occurs over the weekends of May to August and during a 2-week summer vacation, meaning that individuals get more than half their total sun exposure for an entire year in just 46 days—a mere 12% of the 365 days of the year.

The current medical literature offers a great many studies linking vitamin D insufficiency to disease processes like osteoporosis.[10] Recent studies state that vitamin D also performs important functions in the immune system, fundamentally through interaction with dendrite cells where it acts on the secretion of interleukins. This process promotes a type-2 helper T cell response that inhibits the T-cell mediated autoimmune response. Thus, vitamin D deficiency has implications for autoimmune diseases like irritable bowel syndrome, systemic lupus erythematosus, type 1 diabetes mellitus, multiple sclerosis, and rheumatoid arthritis.

The mixed bag of diseases in which vitamin D deficiency may play a pathogenic role includes certain tumors[11] (breast, ovary, colon, prostate, and myeloma) where there is evidence of an inverse relationship between incidence rates and the degree of sun exposure. It is important to

note that paradoxically higher post-diagnosis sun exposure and vitamin D counts are associated with higher survival rates in melanoma.[12]

Psoriasis is a dermatological complaint often speculatively linked with vitamin D deficiency. Topical analogs of vitamin D are effective in the treatment of psoriasis and the beneficial effect of narrow band UV-B phototherapy could be partly explained by a local increase in synthesis of the vitamin. The known relationship between metabolic syndrome and serious psoriasis could be mediated by this mechanism. Moreover, a strong link has been established between vitamin D deficiency and metabolic syndrome and with obesity in particular. Some authors have developed the theory that vitamin D acts to regulate body mass and that reduced intake of ultraviolet radiation prior to the winter helps the mammalian body prepare for hibernation by laying down fat. Vitamin D deficiency is often associated with a tendency to obesity and has also been linked to hypertension, insulin resistance, and cardiovascular disease. However, the results of some studies need further analysis if confounding factors are to be excluded. Finally, there is a possibility that vitamin D may be implicated in mental disorders such as autism or depression, conditions such as chronic pain and fibromyalgia, and an ever-increasing list of other pathologic processes but these speculations must be carefully scrutinized for the time being.

Dermatologists have a clear responsibility to prevent skin cancer by advising the public on sun-exposure behaviors. There is already a strong proven link between sun exposure and skin cancer, especially in cases of intensive exposure over short periods of time leading to melanoma. We believe recent publications linking vitamin D deficiency to pathologic processes do not yet provide sufficient grounds for us to recommend greater sun exposure.

A more sensible response to the new evidence would lead dermatologists to encourage adequate vitamin D levels through dietary supplements calibrated to individual populations and personalized risk of deficiency. We should not run unnecessary risks by recommending greater sun exposure to fair skinned groups that may incur risk of skin cancer. However, adequate levels of vitamin D cannot easily be maintained exclusively on the basis of dietary supplements and certain individuals appear unable to achieve a sufficient minimum from either natural sources or supplemented dairy products. Perhaps a better approach would be to measure calcidiol levels in at-risk populations and prescribe additional supplements wherever necessary. The margin between therapeutic benefit and possible calcidiol intoxication (>150 ng/dL) does however appear relatively narrow. Some evidence of this can be seen in the United States where poisoning induced by excessive vitamin D supplementation following World War II has left a legacy of stricter legislation than in the European Union. Furthermore, individual responses to oral supplements appear to vary widely and stable levels can only be maintained with regular supervision and testing.[13] It is still unclear why vitamin D deficiency is so widespread in populations where sufficient sun exposure and/or oral supplementation are already in place.

We conclude that vitamin D is still a highly controversial issue as many of the published findings may be merely anecdotal. In particular, we conclude that it is not yet appropriate for us recommend more sun exposure to our patients in spite of the recent suggestions. Instead, we must closely monitor the matter over the coming years until we are provided with greater clarification of the functions of vitamin D and the effects of low levels. Finally, returning to our opening quotation from Huxley, perhaps we should add to that statement and say: "science commits suicide when it adopts a creed, but to adopt one with haste is even worse."

Conflict of Interest

The authors declare that they have no conflicts of interest.

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