Osteoporosis & Physical Activity

De Martinis and Ginaldi, J Osteopor Phys Act 2014, 2:2
http://dx.doi.org/10.4172/2329-9509.1000e110

Editorial Open Access

Rethinking the "Sunshine" Vitamin

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The classical, hormonal actions of Vitamin D are related to mineral metabolism and skeletal health. Vitamin D enhances intestinal calcium and phosphate absorption, stimulates osteoclast differentiation and calcium resorption from bone and promotes mineralization of the bone matrix. First evidence for the positive effect of Vitamin D intake for human health came from early studies on rickets and osteomalacia. Over the last decade, the perspective on how Vitamin D influences human health has changed dramatically based on the finding that the Vitamin D Receptor (VDR) and the Vitamin D activating enzyme 1-α-hydroxylase (CYP27B1) are expressed in many cell types which are not involved in bone and mineral metabolism, such as intestine, pancreas, prostate and cells of the immune system. This suggests an important impact of Vitamin D on a much wider aspect of human health than previously known. Especially in the field of human immunology, the extra-renal synthesis of the active metabolite calcitriol—$1,25(OH)_2D$—by immune cells and peripheral tissues has been proposed to have immunomodulatory properties similar to locally active cytokines. Vitamin D plays several roles in the body, influencing bone health as well as serum calcium and phosphate levels. Furthermore, Vitamin D may modify immune function, cell proliferation, differentiation and apoptosis [1,2].

There have been more scientific articles published about Vitamin D in the 21st century than about any other Vitamin, reflecting the massive expansion of the field of Vitamin D research. Adequate Vitamin D status has been linked to decreased risks of developing specific cancers, including cancers of the esophagus, stomach, colon, rectum, gallbladder, pancreas, lung, breast, uterus, ovary, prostate, urinary bladder, kidney, skin, thyroid, and hematopoietic system (e.g., Hodgkin's lymphoma, non-Hodgkin's lymphoma, multiple myeloma); bacterial infections; rheumatoid arthritis; Crohn's disease; periodontal disease; multiple sclerosis; asthma; type 2 diabetes; cardiovascular disease; stroke; peripheral artery disease; hypertension; chronic kidney disease; muscle weakness; cognitive impairment; Alzheimer's disease; clinical depression; and premature death. On the other hand, inadequate Vitamin D status during human pregnancy may be associated with increased risk for the development of type 1 diabetes in the offspring. However, this point of view may be excessively optimistic. There also is evidence that despite the current heavy reliance on serum 25-OHD concentration for the diagnosis of an individual's Vitamin D status, local tissue Vitamin D intoxication may be present in individuals with much lower serum 25-OHD concentrations than are currently appreciated [3]. Only rarely are the symptoms of local tissue Vitamin D intoxication associated with Vitamin D status or intake. An individual's serum 25-OHD concentration may appear to be "low" for reasons totally independent of sunlight exposure or Vitamin D intake [3]. Serum 25-OHD concentration is only poorly responsive to increases in Vitamin D intake, and the prolonged routine consumption of thousands of international units of Vitamin D may interfere with the regulation of phosphate homeostasis by fibroblast growth factor-23 (FGF23) and the Klotho gene product, with consequences that are detrimental to human health [3]. In light of these counterbalancing observations, curbing excessive enthusiasm for universally increasing Vitamin D intake recommendations may be in order [3]. According to recent studies, a Vitamin D deficiency [serum 25(OH)D<20 ng/mL] is likely to be an important etiological factor in the pathogenesis of many chronic diseases. These include autoimmune diseases (e.g., multiple sclerosis, type 1 diabetes) inflammatory bowel disease (e.g., Crohn disease), infections (such as infections of the upper respiratory tract), immune deficiency, cardiovascular diseases (e.g., hypertension, heart failure, sudden cardiac death), cancer (e.g., colon cancer, breast cancer, non-Hodgkin's lymphoma) and neurocognitive disorders (e.g., Alzheimer disease) [4]. Vitamin D is a key nutrient for both healthy children and those with chronic illnesses. Understanding its roles in health and disease has become one of the most important issues in the nutritional management of children. Formal guidelines related to nutrient requirements for Vitamin D in healthy children, recommending dietary intakes of 400 IU per day for infants and 600 IU per day for children over 1 year of age, were released by the Institute of Medicine in November 2010. However, application of these guidelines to children with acute and chronic illnesses is less clear [5]. Physical frailty can potentially be prevented or treated with specific modalities, such as exercise, protein-calorie supplementation, Vitamin D, and reduction of polypharmacy [6]. Vitamin D3 is made in the skin from 7-dehydrocholesterol under the influence of UV light. Vitamin D2 (ergocalciferol) is derived from the plant sterol ergosterol. Vitamin D is metabolized first to 25 hydroxy Vitamin D (25OHD), then to the hormonal form 1,25-dihydroxy Vitamin D (1,25(OH)2D). CYP2R1 is the most important 25-hydroxylase; CYP27B1 is the key 1-hydroxylase. Both 25OHD and 1,25(OH)2D are catabolized by CYP24A1. $1,25(OH)_2D$ is the ligand for the Vitamin D receptor (VDR), a transcription factor, binding to sites in the DNA called Vitamin D response elements (VDREs). There are thousands of these binding sites regulating hundreds of genes in a cell-specific fashion. VDR-regulated transcription is dependent on comodulators, the profile of which is also cell specific. Analogs of 1,25(OH)2D are being developed to target specific diseases with minimal side effects [7]. Vitamin D may come from three potential sources: nutritional sources, UVB-dependent endogenous production and supplements. In humans, Vitamin D is mainly synthesized in the skin after exposure to UVB whereas only a minor part is derived from dietary sources. Very few natural, non-fortified products such as fatty fish (salmon, mackerel, sardines, cod liver oil) or some types of mushrooms (Shiitake), especially if sundried, contain relevant amounts of one of the two major forms, cholecalciferol (Vitamin $D_{3)}$ or ergocalciferol (Vitamin D_2). Some countries like the United States and Canada fortify staple products such as dairy products

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Received February 27, 2014; **Accepted** March 03, 2014; **Published** March 06, 2014

Citation: De Martinis M, Ginaldi L (2014) Rethinking the "Sunshine" Vitamin. J Osteopor Phys Act 2: e110. doi:10.4172/2329-9509.1000e110

with Vitamin D. Thus, the individual Vitamin D dietary intake is highly dependent on nutritional habits, and the country's fortification strategy. However, a review with a global perspective found that 6 to 47% of Vitamin D intake may come from dietary supplements. Consequently, without supplementation, Vitamin D status strongly depends on endogenous Vitamin D production which is also influenced by genetic determinants, latitude, season, skin pigmentation and lifestyle such as the use of sunscreen and clothing. Because Vitamin D levels have been shown to depend on season, this factor should be taken into account when interpreting an individual's Vitamin D status. Individual 25(OH) D levels reach their lowest levels after winter and their maximum at the end of summer. Interestingly, this seasonal variation resembles the described seasonal variation of some infectious diseases including sepsis. Recommendations from national health authorities for optimal serum 25(OH)D levels differ in many countries. Currently, no international consensus is available on the optimal level for Vitamin D supplementation, in particular on the safe upper level. While the tolerable upper daily limit given by the Endocrine Society is 10,000 IU, the more conservative Institute of Medicine (USA) considers a supplementation of up to 4000 IU/day to be safe. The European Food and Safety Authority currently recommends to stay below 4000 IU/day (100 μg). (2) New trials evaluating the effects of Vitamin D supplementation have failed to reveal any robust clinical benefits beyond its known actions on mineral and bone disease [8]. The global market of Vitamin D, according to data released by Euromonitor International, is one of the most lucrative and rapidly expanding in the sector of "nutraceuticals": of all Vitamin and dietary supplements, Vitamin D has posted the highest growth rate since 2007 by a substantial margin with a 20% Compounded Annual Growth Rate (CAGR). The discovery of Vitamin D as an essential nutrient for skeletal development a century ago was a major public health victory. Supplementation, whether solar or dietary, prevented the devastating effects of rickets in children. Five decades later, the molecular mechanisms of the Vitamin's active form (1,25-dihydroxy Vitamin D) and its receptor (Vitamin D receptor [VDR]), were elucidated, and subsequently clinical investigators linked Vitamin D deficiency or insufficiency with osteoporosis. This finding seemed logical because osteomalacia (i.e., the softening of bone in adults due to impaired mineralization) can cause fractures and often coexists histologically with osteoporosis. Slowly, Vitamin D supplementation became established for prevention of osteoporosis. But, as shown in a meta-analysis in The Lancet, the story is more complex, both from an epidemiological and mechanistic perspective [9]. Vitamin D, like calcium, has long been regarded as a fundamental part of the prevention and treatment of osteoporosis. Findings from recent meta-analyses of Vitamin D supplementation without co-administration of calcium have not shown fracture prevention, possibly because of insufficient power or inappropriate doses, or because the intervention was not targeted to deficient populations. There is very little evidence of an overall benefit of Vitamin D supplementation on bone density. Despite these data, almost half of older adults (older than 50 years) continue to use these supplements. Continuing widespread use of Vitamin D for osteoporosis prevention in community-dwelling adults without specific risk factors for Vitamin D deficiency seems to be inappropriate [10]. The guideline from the U.S. Preventive Services Task Force (USPSTF) concludes that the current evidence about calcium and Vitamin D supplementation to prevent fractures in adults is essentially insufficient [11]. This statement may be partly based on the limited efficacy of calcium and Vitamin D supplementation in preventing fractures from skeletal adaptation to mechanical loading, although Vitamin D promotes calcium absorption in the gut and supports bone mineralization that is essential for skeletal stiffness. Bone responds to the local mechanical environment at each skeletal site, as evidenced by marked bone gain in the dominant arms of professional tennis players or rapid bone loss in the weight-bearing sites of astronauts during space flight; it has been considered that the skeleton adapts to mechanical stimulation through control of bone strength by resulting elastic deformation (strain) of bone. It can be hypothesized that the effect of osteoporosis therapy is limited by the natural homeostatic system in the skeleton. This hypothesis is consistent with rapid resolution of the effects of most osteoporosis drugs except bisphosphonates that bind to bone mineral and could partly explain the limited effect of calcium plus Vitamin D supplementation on fracture prevention. Vitamin D supplementation, however, is an open area of investigation, particularly in deficient persons. Clinical trials have been equivocal and sometimes contradictory. For example, supplemental Vitamin D, which might prevent falls in older persons, reduced the risk for falls in a few trials, had no effect in most trials, and increased falls in one trial. Although future studies are needed to clarify the appropriate use of Vitamin D supplementation, current widespread use is not based on solid evidence that benefits outweigh harms [12]. In conclusion, for the sunshine Vitamin, it seems that we should start a new sunrise and determine how the day goes on.

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