Extra-Skeletal Benefits, Endocrine Functions, and Toxicity of Vitamin D
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Abstract
During the past 15 years, the knowledge related to vitamin D has markedly expanded, especially with reference to the hormonal and extra-skeletal effects of vitamin D. The understanding of the biological and physiological functions of 25-hydroxyvitamin D [25(OH)D] and its active hormone, 1,25-dihydroxyvitamin D [1,25(OH)2D] in humans has expanded significantly. The serum 25(OH)D level is the best indicator of vitamin D status. However, in certain groups of people, such as those who are overweight or obese or have type 2 diabetes or metabolic syndrome, the serum 25(OH)D levels may not reflect accurately, the storage amounts of vitamin D in the body. The 1,25(OH)2D level, on the other hand, is not a marker for vitamin D status and thus, should not be measured routinely. The parent (basic) form of vitamin D (not analogs) is the choice for supplementation. Vitamin D analogs, including activated forms, should be reserved for those, whose bodies cannot generate active vitamin D compounds because of end-organ failure, such as liver or kidney disease.

Introduction
Humans are evolutionarily, genetically, and physiologically designed to obtain a major portion of their vitamin D requirement through skin exposure to ultraviolet light (i.e., generation of vitamin D3) [1]. Oily fish, such as salmon and mackerel, contain reasonable amounts of vitamin D [25(OH)D], but only a small proportion of the population regularly consumes these expensive foods in quantities sufficient to receive adequate amounts of vitamin D. Mushrooms are the only non-animal food source that contains notable amounts of vitamin D; the vitamin levels increase as mushrooms are exposed to sunlight prior to cooking [2].

Humans are supposed to generate around 5,000 to 10,000 International Units (IU) of vitamin D daily, depending on the skin surface area and body weight [3-5]. In light-skinned persons this can be achieved with reasonable body exposure to sunlight for 30 to 40 minutes [3,6,7]. However, depending on the condition of the skin (e.g., skin of a younger person versus that of an older person), the skin color, and time of day, it can take longer time to generate such amounts. Any excess vitamin D produced is stored in the liver and fatty tissues for later use.

Obtaining vitamin D through exposure to sunlight is the best option
Consuming vitamin D supplements is not the best choice if one has the opportunity to get exposed to natural sunlight. In addition to being a precursor for its active hormonal form for its endocrine/autocrine functions, 25-hydroxyvitamin D [25(OH)D] is also has independent physiological effects in the body. However, because the unphysiological high peak blood levels achieved with very high-doses of supplementation that revert to deficiency status within 3 to 4 months, and in light of the significant pain associated with intramuscular administration, parenteral administration of high-dose vitamin D (e.g., 325,000 IU) should be discouraged.

This product is not available in the United States of America and is not approved by the Food and Drug Administration. However, it is one of the cheapest forms of vitamin D available in most countries. Thus, if available in the formulary, it can be administered “orally” to rectify vitamin D deficiency with follow-up care with safe sun exposure and/or maintenance doses of oral vitamin D.

Exposure to sunlight has broader beneficial effects than the generation of vitamin D alone, so unless an individual is taking medications that sensitize skin to sunlight exposure or such exposure exacerbates a disease, such as lupus, total avoidance of sun is not a healthful option. In most people, exposure to sunlight and vitamin D supplements are both needed [1]. Vitamin D is involved in the tight regulation of calcium and phosphate levels in the blood and their balance in the body, which are essential for physiologic mineral metabolism and many other functions.

However, the discovery of the presence of vitamin D receptors and the 1α-hydroxylase enzyme that converts 25(OH)D to its active hormonal form, 1,25-dihydroxyvitamin D [1,25(OH)2D] outside the kidneys and skeletal tissues, has led to the development of new hypotheses and investigations into broader actions of vitamin D. A recent investigation of the connections between chronic diseases and vitamin D reported a high risk of chronic disease development in subjects with vitamin D deficiency [8]. Authors concluded that currently there
is insufficient evidence to recommend routine supplementation of vitamin D as a treatment of chronic diseases, but the treatment is desirable in the quest to reduce the risk of chronic disease development [8].

Several large, randomized controlled clinical trials are under way to assess the relationships between vitamin D and several chronic diseases. However, none of these studies are designed to address specific vitamin-D-related hypotheses or investigate the hard end point that is directly related to normalizing serum vitamin D levels. Unfortunately, because of the inherent faulty designs of these clinical studies (e.g., [9]), making firm or useful conclusions will not be possible.

**New knowledge related to the extra-skeletal effects of vitamin D**

Before 1998, there were only two widely accepted functions for vitamin D: calcium homeostasis and skeletal integrity (i.e., bone mineral metabolism). However, in recent years, scientists have recognized that 25(OH)D and its active hormonal form, 1,25(OH)₂D, have other biological activities and physiological functions.

The extra-skeletal physiological functions of vitamin D include cardiovascular and pulmonary functions, regulation of blood pressure and inflammation, modulation of the immune system, metabolic and cellular functions, and cell proliferation. In addition, vitamin D is known to modulate gene expression, second messenger systems, hormonal actions, and the cell cycle and induce apoptosis. For example, vitamin D induces differentiation and inhibits proliferation of various normal and cancer cells, while evidence suggests for different roles of vitamin D and of its active metabolites in other tissues [10].

Having insufficient vitamin D levels for long periods is linked to many pathological disorders and dysregulation of metabolic pathways, including but not limited to derangement of calcium homeostasis, vulnerability to bacterial (e.g., tuberculosis) and viral (e.g., influenza) infections, increased incidence and severity of autoimmune diseases (e.g., multiple sclerosis, type 1 diabetes), dysfunctional and uncoordinated fibroblast growth factor-23-Klotho system, dysregulation of metabolic and hormonal systems (e.g., metabolic syndrome, type 2 diabetes, hypertension, and obesity), and the synthesis and release of hormones (e.g., insulin, rennin-angiotensin-aldosterone system) [11,12].

**Endocrine effects of vitamin D**

Vitamin D has multiple endocrine functions, and its actions are demonstrable in most cells and in all organs. The effects of vitamin D on musculoskeletal tissues, such as improving balance, reflexes, muscle function, and coordination; bone mineral metabolism; and reducing the loss of muscle fibers, are well established. The most active molecular form of vitamin D, secosteroid 1,25(OH)₂D, is produced predominantly in the renal tubules and acts throughout the body; thus, it is considered a hormone. Structures and molecular species of these three forms of vitamin D are illustrated in Figure 2. Through 1,25(OH)₂D-derived endocrine mechanisms, enhancement of intestinal absorption of calcium, mineralization of osteoid tissues, and demineralization of calcified skeletal tissues, and conservation of renal calcium occurs.

The decrease of serum calcium enhances the PTH-mediated osteoclastic bone-resorbing activity, that is designed to rapidly increase calcium efflux into the extra-cellular fluid to maintain serum ionized calcium levels [11,13]. These complex but well-coordinated biochemical and hormonal interactions are designed to maintain tight control of serum ionized calcium levels; they also prevent the occurrence of rickets and osteomalacia.

Vitamin D also has an indirect effect on vascular tone and control of blood pressure through modifying the actions of the renin-angiotensin hormonal system. In addition, through the local synthesis of 1,25(OH)₂D in various extra-renal tissues, vitamin D provides autocrine and paracrine actions, influencing the expression of many genes and modulating several intracellular metabolic pathways [14]. Vitamin D influences these mechanisms and provides beneficial effects on the cardiovascular, respiratory, and other systems. It also enhances the innate and adaptive immune systems, protecting against invading organisms.

**Personalized supplementation with vitamin D**

Vitamin D supplementation should be personalized; such a...
targeted therapy is necessary for overcoming several illnesses and optimizing the health of individuals. The biologically most active form of vitamin D, 1,25(OH)D, regulates more than 1,000 genes within the human genome. The mechanism of action is further modulated by gene polymorphisms and epigenetics. The study and the knowledge-based metabolomics, transcriptomics, and epigenetics of vitamin D and its supplementation hold promise for generating better personal and community-based clinical outcomes in the future [15].

Considering the broader actions, clinicians have to seek and define the “adequate” physiological levels of vitamin D and the vitamin D supplementation needed to attain optimal serum 25(OH)D levels in individual and on population basis [16,17]. Such studies and recommendations should define the “median” serum 25(OH)D levels needed to lower the incidence of chronic diseases; not merely the “minimal” levels.

The minimum 25(OH)D levels required to prevent different diseases

It is important to note that various organs and tissues require different serum levels of 25(OH)D for optimal physiological function and protection of humans from harm. Thus, it is important to understand that the “minimum” serum 25(OH)D levels suggested by the United States Institute of Medicine (IOM; e.g., 20 ng/ mL [18,19]) and by The American Endocrine Society [3] (30 ng/ mL) (Figure 3) are for preventing harm on mineral metabolism (i.e., preventing rickets and osteomalacia) in humans. However, these levels are not same as that which is needed for the prevention of other chronic diseases such as cardiovascular disease, autoimmune diseases, cancer etc. The latter groups of diseases require a minimum serum 25(OH)D level of 40 ng/ mL to have a meaningful, positive impact of the disease.

Targeted therapy and the use of vitamin D analogs

Synthetic analogs of vitamin D are recommended only for those who do not have the capacity to activate the parental (basic) vitamin D to its active forms. For example, instead of basic vitamin D, the use of the 25-hydroxylated form, 25(OH)D is necessary for patients with liver failure; 1α(OH)D or 1,25(OH)D is needed for those with renal failure; and 1,25(OH)D is needed for those with failure of both liver and kidney. The goal of targeted analogue therapy is to bypass the need for activation of parental vitamin D molecules in a failing organ, enabling patients to generate its active hormone, 1,25(OH)D (Figure 2). The use of vitamin D analogs in other circumstances such as the treatment of vitamin D deficiency, osteoporosis, rickets, or osteomalacia, or their use as a supplement is inappropriate and not justified. This is not only because analogs are expensive (i.e., several-fold higher cost) but also because the 25(OH)D molecule itself has independent beneficial effects, and the analogs are associated with significantly higher incidences of adverse effects, such as hypercalcemia and hypercalciuria [20].

Recommendations and Guidelines

In 2012, the IOM increased the Recommended Dietary Allowance (RDA) of vitamin D for all age groups, which was a step in the right direction [19]. However, the recommendations are far lower than those needed to reach an optimum, physiological vitamin D status and thus are not useful for many persons. In addition, the recommendations made are specifically for those living in North America, for public health purposes [21] and thus are not applicable for individual persons, patients, or people living outside North America [1,22,23]. Moreover, the 2012 IOM recommendations for daily intakes and serum 25(OH)D levels were based only on “skeletal physiology” [21] and thus, are inappropriate for generalizing.

The guidelines from the US Endocrine Society are for individual patients (Figure 3) but, do not address the needs of special or vulnerable groups [3]. Subsequent guidelines by other groups have addressed this lack of knowledge in subsets of the vulnerable population with high incidences of vitamin D deficiency [22-24]. For example, to aid in the prevention of cardiovascular and pulmonary disease; insulin resistance, type 2 diabetes, obesity, cancer, and autoimmune diseases; and for those with intellectual, neurological, and developmental disabilities, the minimum serum 25(OH)D level of 40 ng/ mL is recommended, with an optimal range between 40 and 60 ng/ mL [22-27]. Thus, the goal is to achieve a blood level of 25(OH)D levels of 40-60 ng/ mL [10,27-29].

The recommendation of the latter value was in part based on correlations of serum 25(OH)D levels with various disease statuses and the vitamin D status in sun-exposed tribes in Africa, such as the pastoral Masai and the hunter-gatherer Hadza. The mean serum 25(OH) vitamin D levels in these tribes are 46 ng/ mL with little fluctuation [30] (i.e., few or none had vitamin D deficiency in these communities). The dark melanin pigmentation (the original skin color of human beings) in the skin of these African descendants [29] in part, prevents over-production of vitamin D in the skin but more importantly prevents the skin damage and skin cancers caused by excessive UV ray exposure.

It would be interesting and useful to carry out epidemiological/ecological studies in these communities to assess the prevalence and severities (if any) of cardiovascular, pulmonary, autoimmune diseases, and causes of deaths that can be correlated with serum 25(OH)D levels in these populations. Their life expectancy is somewhat lower, but this is due to causes other than those
Adverse effects caused by vitamin D

Adverse effects associated with vitamin D supplementation are rare and should not be diagnosed solely on the basis of an elevated 25(OH)D serum level [31]. The manifestation of vitamin D deficiency is a clinical syndrome that consists of markedly elevated serum 25(OH)D levels more than 125 ng/ mL (> 300 nmol/ L) and is associated with hypercalcemia, hypercalciuria, and suppressed parathyroid hormone levels [11,13]. Most of the signs and symptoms of this syndrome is related to the elevated serum ionized calcium levels.

Three key parameters of this syndrome (hypercalcemia and hypercalciuria and, consequent clinical signs and symptoms) are due to, (a) prescription errors or individuals mistakenly taking supra-pharmacologic doses of vitamin D supplements for a prolonged period, (b) overdosing with parenteral injections (i.e., thus, lack of feedback control), and (c) extra-renal activation of the 1α-hydroxylase enzyme (e.g., in granulomatous tissues, such as in sarcoidosis). Healthcare workers should investigate the personal history, background, and the needs of patients along with biochemical variables to assess the status of vitamin D, so that benefits are maximized while adverse effects are prevented [32].

Conclusion

The currently recommended daily allowance of 600 to 800 IU vitamin D is inadequate for increasing or maintaining an adequate serum 25(OH)D level of 30 ng/ mL. In the absence of adequate exposure to sunlight, most individuals require a daily oral intake of at least 1,000 IU (25 μg; ranging from 1,000 to 5,000 IU/ day) of vitamin D3 [3,16,17,27,33] to raise and maintain the blood 25(OH)D level above 30 ng/ mL (75 nmol/ L), so that the blood level remains within the physiological range of 30 to 50 ng/ mL.

Current data suggest that maintaining blood levels of 25(OH)D between 30 and 50 ng/ mL over a long period is necessary to result in meaningful decreases of morbidities from several communicable and non-communicable diseases and reduce the severity of existing diseases. Because the costs associated with supplementing oral vitamin D are minimal (e.g., less than $12/ year, per person) [27], such treatment is likely to be a highly cost-effective way of preventing chronic diseases. Nevertheless, there are no convincing data available from randomized controlled clinical trials, validating this yet.

References

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