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Review Article

Effective and Practical Ways to Overcome Vitamin D Deficiency

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INTRODUCTION

Globally, the prevalence of vitamin D deficiency is high, and the incidence is rising. This common micronutrient disorder is easily reversible; so, as the associated morbidity and mortality among affected people. The incidences of vitamin D deficiency continue to increase and have become a pandemic, mostly because of insufficient exposure to sunlight. Most of the vitamin D needed by humans is generated in the skin after exposure to ultraviolet B (UVB) rays.

However, overexposure to sunlight does not cause hypervitaminosis D because of the presence of negative feedback systems in the skin [1]. However, repeated sunburns could cause damage to skin and DNA in skin cells, accelerate aging of the skin, and increase the risk of common forms of skin cancer [2]. Intriguingly, the incidence of melanoma, the most dangerous form of skin cancer is reduced with sun exposure [3]. This brief article focuses on the cost-effective modes of administration of oral vitamin D and its benefits.

Vitamin D deficiency

Vitamin D is essential for life, including for reproduction, fetal growth, and immunity, and proper functioning of all body systems [4]. Previtamin D is synthesized in the skin from 7-dehydrocholesterol after exposure to ultraviolet B (UVB) rays. Cholecalciferol (vitamin D_3) is the chemical form of vitamin D derived from animal sources, while ergocalciferol (vitamin D_2) is derived following UVB irradiation of plant steroid, ergosterol.

Vitamin D binds to the D-binding protein prior its transportation to the liver. Both vitamin D_3 and D_2 are transported to the liver following binding to vitamin D binding protein and hydroxylated to 25(OH)D via hepatic, 25-hydroxylase enzyme (CYP2R1); the major circulating and storage form of vitamin D. 25(OH)D is subjected to a second hydroxylation in the kidney to form the most biologically active form, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D; calcitriol]. Calcitriol is generated mostly in renal tubular cells but also generated within the target tissue cells that are critical for intracellular functions [5].

Generation and replenishment of vitamin D

In general, food provides less than 20% of the human body's vitamin D needs. Thus, for an average person, it is nearly impossible to get adequate amounts of vitamin D from the diet alone. Many people also are not getting adequate exposure to sunlight for various reasons. In such persons, oral administration of supplementary vitamin D_3 is reasonable and a cost-effective way to maintaining health. The American Academy of Dermatology advocates avoiding exposure to ultraviolet sunrays and depending on dietary constituents for vitamin D [6]. However, this advice may not be applicable for the majority of people.

The best way to obtain vitamin D is to have daily, safe sun exposure. Because of geographic location of residence, sun avoidance behavior, and a number of other reasons, relatively small percentage of people have the ability to do such. Because exposure to sunlight is the main source of vitamin D, most vitamin D deficiency occurs in housebound [7], in older people, and those who avoid exposure to sunlight [8]. The latter includes, the overuse of sunscreens, clothing, and working indoors [9,10].

Because UVB skin penetration is inversely reduced with skin pigmentation, together with the sun avoidance behavior, inhabitants living closer to the equator, such as in Africa, the Indian subcontinent, and the Middle East, also have a higher incidence of vitamin D deficiency [11,12]. Common causes of vitamin D deficiency such as, sun avoidance/ insufficient exposure to sunlight, metabolic disorders, obesity, and malabsorption syndromes are highlighted in the Figure 1.

Vitamin D supplements

The two forms of vitamin D that have been available as supplements; ergocalciferol (D_2) and cholecalciferol (D_3). Of these, vitamin D_3 is the preferred form as a supplement; it is chemically identical to the vitamin D produced by the body. In addition, vitamin D_3 has a longer half-life than does vitamin D_2 and maintains the serum 25(OH)D concentration over a longer period.

It is preferable to administer vitamin D as a daily maintenance dose rather than administering higher doses infrequently [13,14]. Doses administered too infrequently (e.g., less than once a month) and extremely high doses (e.g., upward of 300,000 IU) given intermittently are ineffective and may even have adverse effects [15]. The use of doses over 300,000 I.U., administered once or twice a year has reported to increase falls and fractures

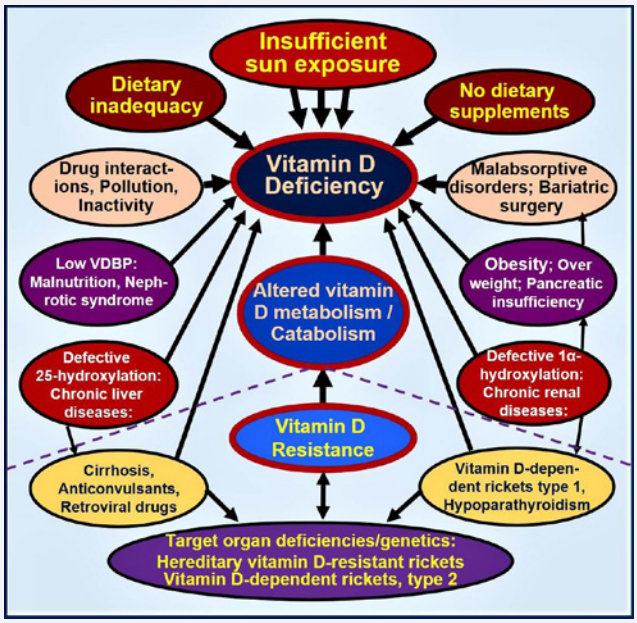

Figure 1 The top part of the figure illustrates the three common causes of vitamin D deficiency, interactions, and common conditions that are likely to deteriorate with vitamin D insufficiency and deficiency. Bottom part (below the dashed line) of the figure highlights the rare genetic abnormalities associated with vitamin D resistance and cause deficiency status and different types of rickets.

[15]. Although this is not due to a direct toxicity of vitamin D, the rapid increase of serum vitamin D concentration provides a feeling "good" effect within the first few days, which leads to recipients increasing their physical activities too soon, causing falls and fractures.

Vitamin D in injectable forms are dissolved in oil and such injections are painful; thus, should be avoided. In addition, there is no advantage of administering intramuscular vitamin D, when gastrointestinal absorption via the oral route is satisfactory in more than 99.5% of the population. Moreover, supra high doses of vitamin D administered infrequently, reported to have adverse effects [16,17].

While injectable form (i.e., glass vials containing higher than 300,000 IU/mL, per vial) of vitamin D vial are not available in north America, are available in many other countries. Nevertheless, when 50,000 IU vitamin D capsules are not available, contents of the mentioned vials can be effectively administered orally (an economic way), as part of an up-front high dose, loading strategy.

Effective ways of replenishing vitamin D

Persons with serum 25(OH)D concentration less than 20 ng/mL are benefited by a loading dose of between 200,000 and 1.3 million IU, administered over a several weeks. This mode of administration will allow achieving adequate serum 25(OH)D concentrations and replenish body vitamin D stores rapidly, in persons with vitamin D deficiency. There are no adverse effects, when the right totals dose is administered orally, spread over several weeks. This, a cost-effective, up-front oral loading dose should be considered in persons with vitamin D deficiency, which would help them to recover quickly. There are many ways of doing such. A simplified flow chart for administration of vitamin D is illustrates in the Figure 2.

The easiest is to administer of one gel-capsule containing 50,000 IU, once or twice a week for several weeks, as appropriately. The total dose needed is calculated based on the baseline serum 25(OH)D concentration and the body weight [18,19] Such doses are safe and do not cause any adverse effects [20,21].

In the absence of giving loading doses to persons with vitamin D deficiency, such persons likely require several years to achieve an adequate body storage level. During that period, they are unnecessarily vulnerable to other diseases. Thus, it is best to avoid delay in achieving vitamin sufficiency. For example, those with serum 25(OH)D concentrations of less than 15 ng/mL may require between 400,000 IU and 1.2 million IU of vitamin D depending on the serum 25(OH)D concentration and the body weight to refill tissue storage. The next section provides a few examples.

Examples of loading doses of vitamin D and maintenance doses

The goal of the loading dose regimens is to rapidly rectify deficiency status and replenish vitamin D storage in tissues, without subjecting the recipients to adverse effects. For examples, those with vitamin D insufficiency (between 20 and 29 ng/mL) could be supplemented with a relatively smaller loading dose (i.e., 100,000 or 200,000 IU, using 50,000 IU gel capsules as described above) or with an appropriate daily dose of oral vitamin D exceeding 2000 IU/day.

Whereas a person with a vitamin D level of 10 to 15 ng/mL needs a total loading dose of more than 600,000 IU to replenish body stores and restore blood levels. Such can be provided with a capsule of 50,000 IU twice a week for 6 weeks (or one capsule a week for 12 weeks, but some may need a repeat of the course), followed by a maintenance dose of at least 2,000 IU/day. Those with levels of less than 7 ng/mL might require between, 800,000 and 1.2 million IU of vitamin D to replenish body vitamin D stores. Administration of such larger doses should be spread out over a four to five months period.

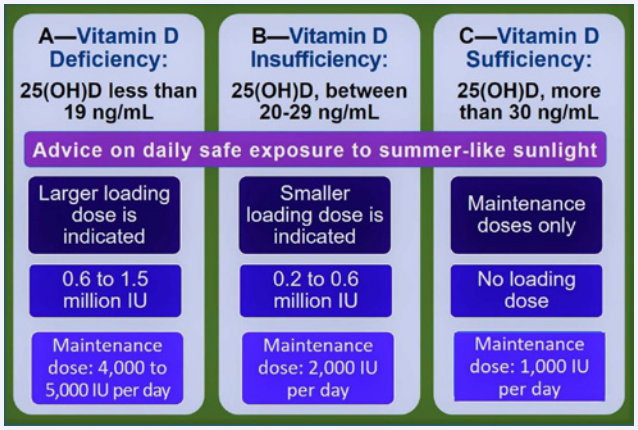

Figure 2 Simplified, schematic illustration of making decision for supplementing vitamin D in persons with deficiency and insufficient and recommended daily maintenance doses.

The need of a daily maintenance dose of vitamin D

The provision of a loading dose itself is not enough for those with vitamin D deficiency. Such individuals are going to need longer term, daily suitable maintenance dose of vitamin D to prevent serum 25(OH)D levels reverting to deficiency status. This daily maintenance dose will assure the maintenance of physiological serum 25(OH)D concentrations and longer-term benefits from the intervention. For example, a person of 70 kg body weight with a serum 25(OH)D concentration of 18 to 24 ng/mL can be treated with either 5,000 IU/day for 2 months or 50,000 IU once a week for 6 weeks, followed by a longer-term maintenance dosage of 2,000 IU/day.

Administration of very large doses, such as doses above 300,000 IU once or several times a year would cause marked fluctuation of serum and intracellular vitamin D concentrations that are not physiological. In contrast, it is safe to administer doses such as 50,000 IU capsules, once or twice a week (depending on the baseline serum 25(OH)D concentration), over a few weeks to bring the serum 25(OH)D concentrations to required level [19,22].

This would allow not only a reasonable intestinal absorption of vitamin D but also steadily replenishing vitamin D stores in the body tissues without having high peaks in the blood. We have been using this upfront loading doses regimens of vitamin D since 2000, without any adverse effects [19-23], allowing a correction of vitamin D concentrations and replenishing the body stores, over a few weeks and to obtain clinical expected beneficial responses [19,22,24].

Those who are severely deficient, with serum 25(OH)D concentrations of less than 10 ng/mL (concomitantly having osteomalacia and proximal myopathy), as described above are likely to have a deficit of between 800,000 and 1.2 million IU. To replenish their body stores, they are likely to need a 50,000 IU capsule twice a week for 8 to 12 weeks, followed by a maintenance dosage between 2,000 and 5,000 IU/day. Table 1 illustrates simple examples of practice ways for correcting vitamin D deficiency using upfront loading doses of oral vitamin D, to normalize—bring serum 25(OH)D above 30 ng/mL and replenish body stores.

In such patients, it is a mistake for a healthcare provider to advise a patient to take over-the-counter vitamin D preparations of 400, 1,000, or even 2,000 IU/day because it would take 2 to 4 years to obtain the needed total amount of vitamin D, not even counting the patient's ongoing daily needs during that period. Therefore, such deficits must be provided within weeks, not in years.

It is notable that vitamin D supplementation is contraindicated (or administer with great caution) for persons who had or has the potential to experiencing hypercalcemia (i.e., increased calcium in blood), hypercalciuria (i.e., excess calcium in urine), or renal osteodystrophy with hyperphosphatemia or hypervitaminosis D. These groups of people include, persons with hyperparathyroidism, granulomatous diseases (e.g., tuberculosis, leprosy, and sarcoidosis), Williams syndrome, and so forth [7,15].

Maintenance of serum concentration, activation and benefits of vitamin D

It is also important that, following an oral loading dose of vitamin D supplement, it is necessary to initiate a daily maintenance dose of vitamin D [25,26]. Because of the longer half-life, large storage capability, and the time taken to establish equilibrium of serum 25(OH)D concentration, physicians should not request repeat measurement of 25(OH)D for at least four months. In few patients, it is likely that concentrations may be still less than required, and if so, one should consider prescribing a second course of 50,000 IU (one capsule) per week, of cholecalciferol (D_3), for 6- to 12-week to replenish body stores and to maintain serum concertation [12,23].

Calcitriol promotes intestinal absorption of calcium and phosphate and extracellular calcium Ca^{2+} homeostasis, directly and through its interaction with parathyroid hormone, and mineralization of the skeleton. The majority of the actions of its hormone, calcitriol, predominantly generated in proximal renal tubular cells.

However, an unquantifiable amount is generated intracellularly in the target tissue cells; both activations occur through the enzyme 1α-hydroxylase (CYP27B1). Vitamin D receptors are present in the nucleus and are ubiquitous, which explain its multiple biological and physiological actions. The target tissue cell generated calcitriol is responsible for many non-musculoskeletal intracellular actions of vitamin D, such as prevention of autoimmunity, infections, cancer etc [27]. This occurs following the activation of its classical nuclear bound VDR. In addition, in certain cells, vitamin D receptors are also found on the cell membranes [28]. The fast acting, non-genomic actions of vitamin D occur following its interaction with this membrane bound receptors [29,30].

Achieving physiological concertation of vitamin D in blood

Evidence supports wider beneficial effects of vitamin D but to achieve such effects, serum 25(OH)D concentrations must be maintained at a level, more than 30 ng/mL [14]. Long-term maintenance of an adequate serum 25(OH)D concentration (e.g., more than 30 ng/mL) has been shown to reduce the incidences and severity of several common medical disorders.

Table 1: Guidance on upfront loading dose regimens to replenish vitamin D stores in the body.

Serum vitamin D (ng/mL)	Frequency of administration (per week)	Duration of therapy (weeks)	Total dose for correction * (IU millions)
≤ 5	100,000 IU, one dose; 50,000 twice a week	14	1.3 to 1.5
6–10	50,000 twice a week	12	1.0 to 1.2
11–15	50,000 twice a week	10	0.8 to 1.0
16–20	50,000 twice a week	8	0.6 to 0.8
21–25	50,000 once a week	10	0.4 to 0.5
26–30	50,000 once a week	6	0.2 to 0.3
Maintenance regimens	50,000 IU, or	Monthly	Maintenance
	1,000 to 2,000 IU	Daily	Maintenance
	4,000 or 5,000	Daily	High risk persons

These include insulin resistance, type 2 diabetes, obesity, complications associated with pregnancy- [31,32], infections, autoimmune disorders, certain cancers [33], impairment of DNA repair, systemic inflammation, and oxidative stress that potentiates metabolic illnesses such as cardiovascular disorders, and premature deaths [4]. It is important to appreciate that b**oth extremes of vitamin D concentration can be harmful and thus should be avoided.Vitamin D deficiency increases comorbidities and severity of complications**

Mounting scientific evidence supports additional beneficial effects of vitamin D outside the musculoskeletal system. Studies show that concentrations of serum 25(OH)D levels of less than 20 ng/mL are sufficient only for the musculoskeletal system [34,35]. In addition, such levels increase the risk of certain acute respiratory tract infections [36-38] and mycobacterial diseases, such as leprosy and tuberculosis [39,40]. Hypovitaminosis D not only increases the vulnerability to these medical disorders but also worsens the severity of existing diseases, including autoimmune disorders, heart disease, and cancer [41].

Evidence suggests that vitamin D facilitates the regulation of blood pressure and cardiac, endothelial, and smooth muscle cell functions, thus, playing an important role in cardiovascular protection [31,42]. In addition, $1,25(OH)_2D$ improves immunity; subdues inflammation; and reduces the incidence and severity of common cancers [33], autoimmune diseases, and infectious diseases [43]. The knowledge of the effects of vitamin D status on extraskeletal tissues is expanding, but recently published, poorly conducted, large scale vitamin D clinical trials have caused confusion [44]. Figure 3 illustrates the generation of calcitriol, modes of obtaining vitamin D, its interactions with multiple systems, which increase risks of deficiency status.

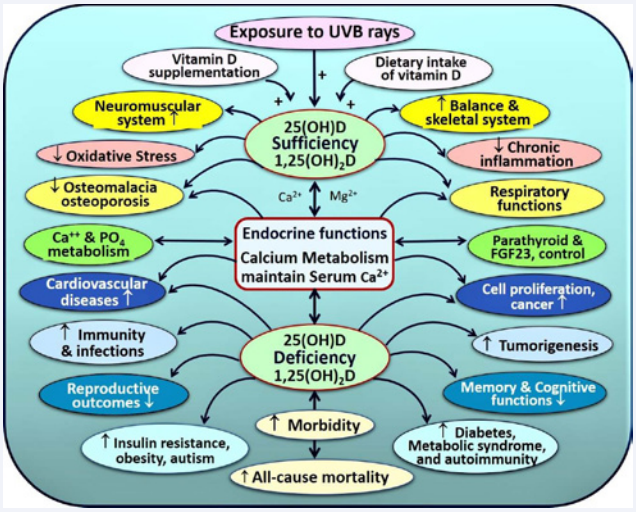

Figure 3 The biological and physiological effects of sufficiency and deficiency of 25(OH)D (calcidiol) and $1,25(OH)_2D$ (calcitriol) in different tissues in the body systems. Figure also illustrates key compounds that directly influence the generation of vitamin D, including Ca^{2+}, Mg^{2+}, parathyroid hormone and fibroblast growth factor-23 (FGF-23). UVB = Ultraviolet rays [modified from Wimalawansa, 2018 (1) and Wimalawansa 2012 (22)].

The use of food fortification as a mean for replenishment of population vitamin D

Micronutrient supplementation (which also can be provided cost-effectively through systematic food fortification programs) consists of a combination of vitamin D (with guidance on safe sun exposure), vitamin K_2, and antioxidant supplements (and other key deficient nutrients, such as calcium and vitamin A); the cost is approximately $25/year per person. If the management chose to use a combined micronutrient supplement that contains approximately 2,000 IU of vitamin D that likely would have even a larger benefit on both employees and the company.

To overcome not only vitamin D deficiency but also micronutrient deficiencies, it is necessary for each country (or ethnic group) to have guidelines and implement them, especially targeted, food fortification programs that are highly cost-effective. Such programs consist of providing one or more of the deficient nutrients and essential micronutrients, such as vitamin D, vitamin A, iron, iodine, or calcium, and targeting specific population groups or the entire country. Target groups can be ethnic or certain cultural groups; those with certain disorders, such as obesity, metabolic syndrome, cancer, or autoimmune disorders [45]; pregnant and lactating women; infants; or the elderly.

Thus, guidelines and recommendations must also encompass modes of safe sun exposure, food fortification strategies for communities, and supplementation guidelines for those who with special needs, as well as, when appropriate, the measuring of serum 25(OH)D concentration [7,11,46,47]. It is advisable that each country or at least groups of countries to have ethnic and culturally specific, vitamin D guidelines that also encompass safe sun exposure, cost-effective food fortification strategies, and vitamin D supplementation recommendations, including for especially for those with special needs

The need for country-specific vitamin D guidelines

Despite ethnic and other variations, the optimal range of serum 25(OH)D concentration for humans does not vary from country to country. Considering ethnic, cultural, dietetic, social, and geographic differences, each country (or region) should consider generating its own guidelines for calcium and vitamin D supplementation, , as well as other essential micronutrients. The focus should be to improve general health, preventing acute and chronic diseases, and to reduce healthcare costs.

The United States and Canada (North America) or European vitamin D-related guidelines are designed and validated only for those populations. Therefore, other countries should not depend on those guidelines. Instead, other countries and regions (e.g., the Gulf region, Asian countries, South America, etc.) should develop their own ethnic-specific, culturally acceptable, vitamin D-related clinical practice guidelines and recommendations for supplementation (together with safe sun exposure guidance) based on the needs of their population. However, progress in this matter has been somewhat hampered by the confusion caused by a few recently published, large clinical trials related to vitamin D; these trials, including the VITAL clinical study, contained multiple study design flaws.

For the benefit of local populations, it is prudent for individual countries, or at least countries within geographic regions, to generate their own country (or region)-specific vitamin D guidelines. This has been successfully done in GULF countries, southern Europeans [48], Poland [43], United Arab Emirates [11], Saudi Arabia [49], persons with neurodevelopment conditions [7], etc. This could be facilitated by adopting best practices from published data and guidelines and considering pertinent ethnic, cultural, and dietary habits, as well as geographic locations with restricted UVB availability. Recommendations also should be given that reflect the increased need for vitamin D during the winter months, when UVB availability is minimal or absent.

With increasing longevity of humans and the need to maintain optimal health, it is important to have adequate intake of micronutrients, including antioxidants. Preferably, these should come from the diet; the goal is to maintain a physiological concentration in the blood and body. Micronutrients such as vitamins, antioxidants, and essential fatty acids ideally should come from natural food sources (but these sources do not *need to be* organic). These nutrients are important for eliminating invading pathogens and preventing autoimmunity and certain cancers.

Cost of replenishing vitamin D stored in the body

Rectifying vitamin D deficiency on average costs less than 0.1% of the cost of investigations and treatment of worsening comorbidities and complications associated with hypovitaminosis D (varies between 0.2% and 0.06%) in an average person. For example, to maintain serum 25(OH)D concentration in the normal range (more than 30 ng/mL) on average costs approximately $12/year per person [27]. However, the average cost for managing a hypovitaminosis-associated disease, such as diabetes, insulin resistance, or obesity, in a person costs between $6,000 and 18,000/year per affected person [27].

Despite the high benefits relative to cost, millions of people continue to have vitamin D deficiency and related complications that otherwise could have been prevented. The individual and the population health can be markedly improved by maintaining serum 25(OH)D concentrations of greater than 30 ng/mL (75 nmol/L), which would improve the quality of life and reduce all-cause mortality [1,50]. However, for prevention of certain diseases and to reduce all-cause mortality, serum 25(OH)D concentrations need to be maintained between 40 and 60 ng/mL [1,27,31,51].

Who needs testing of serum 25(OH)D concentrations

Virtually none of the recent vitamin D clinical practice guidelines recommend screening for vitamin D deficiency in general pubic in the absence of a clinical suspicion or having another good reason, in otherwise healthy population [11,52,53]. This is in part due to the low incidence among this type of populations, high cost of the test, and thus the lack of cost-effectiveness [11,48]. In developing countries and in emerging economies, where the measurement of 25(OH)D testing is expensive or not available, when clinically suspected, it is reasonable and ethical to treat patients with appropriate oral vitamin D doses.

Nevertheless, the measurement of serum 25(OH)D concentration is justifiable for those in high risk groups. The latter includes, those with autoimmune tendency or diseases, recurrent infections, intracellular bacterial infections (e.g., tuberculosis), malabsorption syndromes, taking medications that increase catabolism of vitamin D (e.g., anti-epileptic and anti-retroviral agents, etc.), metabolic derangement syndromes such as obesity, insulin resistant syndrome, diabetes, cancer, as well as pregnant women should be given the opportunity for laboratory measurement of serum 25(OH)D concentrations, prior to commencing on vitamin D replacement therapy [7,11,19,32,48,54].

Although the number of diseases and disorders related to vitamin D deficiency is vast, the cost of investigating and managing the complications associated with disorders is extremely high, estimated to be more than $280 billion annually worldwide. Maintaining serum 25(OH)D concentrations between 30 and 60 ng/mL would significantly reduce the severity of these diseases and prevent complications and markedly reduce costs. The positive impact on benefits in humans and the economy of following the appropriate public health approaches discussed would exceed the benefits derived from the combined targeting of infectious and parasitic diseases.

CONCLUSIONS

The consequences of vitamin D deficiency include proximal (shoulder-girdle) myopathy, rickets osteomalacia, impaired immunity (increase risks for recurrent infections), autoimmune diseases, metabolic disorders (e.g., obesity, metabolic syndrome, and diabetes mellitus), hypertension, pregnancy-associated complications, and higher risks of colon, breast, and prostate cancers. To expedite normalizing serum 25(OH)D concertation and replenishing the body storage, it is best to use an appropriate loading dose of oral vitamin D in those with vitamin D deficiency and insufficiency, followed by a daily maintenance dose. While safe sun exposure is the natural way to obtain vitamin D, a daily maintenance dose or twice a month high dose (e.g., 50,000 IU each dose) basic vitamin D (not activated forms) oral supplements should be given for to those with vitamin D deficiency and who are at risk.

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