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ACHIEVING POPULATION VITAMIN D SUFFICIENCY WILL MARKEDLY REDUCE HEALTHCARE COSTS

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Oxygen, water, and food are three essential components for human survival. Carbohydrates, fats, and proteins are the three major food components; preferably these should be eaten as natural components, unprocessed. Organic food while nutritionally similar to natural food, marketed at a higher price. Beyond that, there are several essential food substances that human life is dependent upon. These include essential fatty acids, macrominerals, and micronutrient components.

These are categorized as essential, as these nutrients cannot be synthesized in adequate amounts within the body. Therefore, sufficient intake is essential for good health and survival. Three main categories of indispensable micronutrients are trace minerals, vitamins, and antioxidants. This review explores the benefits of maintaining population serum 25(OH)D concentrations above the minimum physiologic need.

What is vitamin D?

Vitamin D is a fat-soluble vitamin. Because of their solubility, fat-soluble vitamins should be taken immediately after a meal contacting some fat to stimulate intestinal secretions to enhance absorption. In normal circumstances it is stored in adequate quantities in liver, muscle and fatty tissue. From these storages, vitamin D is gradually release into the circulation to maintain serum concentration. Once 25(OH)D is activated in renal tubules, it released to the circulation as a hormone. The primary function of vitamin D is to tightly maintain serum ionized calcium concentration and support skeletal health through its hormonal form, calcitriol.

Vitamin D supplements should be taken with or immediately after the largest meal to improves its intestinal absorption. This process is reported to increase serum levels of 25(OH)D concentration up to 50% compared to taken at an empty stomach.[1] Vitamin D influences the musculoskeletal system, intestinal absorption of calcium, modulating immune and cardiovascular systems, synthesis of hormones, and controlling the cell proliferation. Enzymes needed to activate 25(OH)D and vitamin D receptors are distributed ubiquitously. Considering these, it is not surprising that hypovitaminosis D can cause an array of medical disorders.

Common causes and functions of vitamin D deficiency

Most people experience vitamin D deficiency because of lack of exposure to sunlight. Although people avoid sun exposure due to many reasons, those who live in northern and southern latitudes do not have the luxury of sunlight for more than half the year. Other potential causes of vitamin D deficiency include climate issues and air pollution, lifestyle, and concerns about skin cancer. Another category is those who are taking medications that increase hepatic catabolism of vitamin D. Examples of such medication include anti-epileptic and anti-retroviral drugs.

Emerging research supports the plausible roles of vitamin D and its active metabolites in protecting a number of diseases, such as cancer, heart disease, fractures and falls, autoimmune diseases, influenza, type 2 diabetes, and depression. Working in conjunction with parathyroid hormone, vitamin D tightly maintain serum ionized calcium and phosphorus concentration and enhancing intestinal calcium absorption. In addition, vitamin D influences the musculoskeletal system particularly skeletal calcification, modulating immune and cardiovascular systems, pancreas and brain functions, synthesis of hormones, and the control of cell cycles.

Biochemistry—generation of vitamin D

Vitamin D is an essential micronutrient for human survival. Its active hormonal form, 1,25 dihydroxy vitamin D [1,25$(OH)_2$D; calcitriol], is generated in renal

tubular cells. Because food contains little vitamin D, humans are expected to generate most of their daily vitamin D requirement through skin exposure to ultraviolet B (UVB) rays in sunlight. The body makes vitamin D after the exposure to UVB rays—photoconversion—of 7-dehydrocholesterol in the skin to previtamin D.

The rate of generation of previtamin depends on multiple factors, including skin color, health of the skin, age, geographic location, time of the day and the year, and the duration of sun exposure. Following hydroxylation in the liver and then in the kidneys, fat-soluble vitamin D is converted into its active form, a functional secosteroidal hormone, calcitriol (Figure 1).

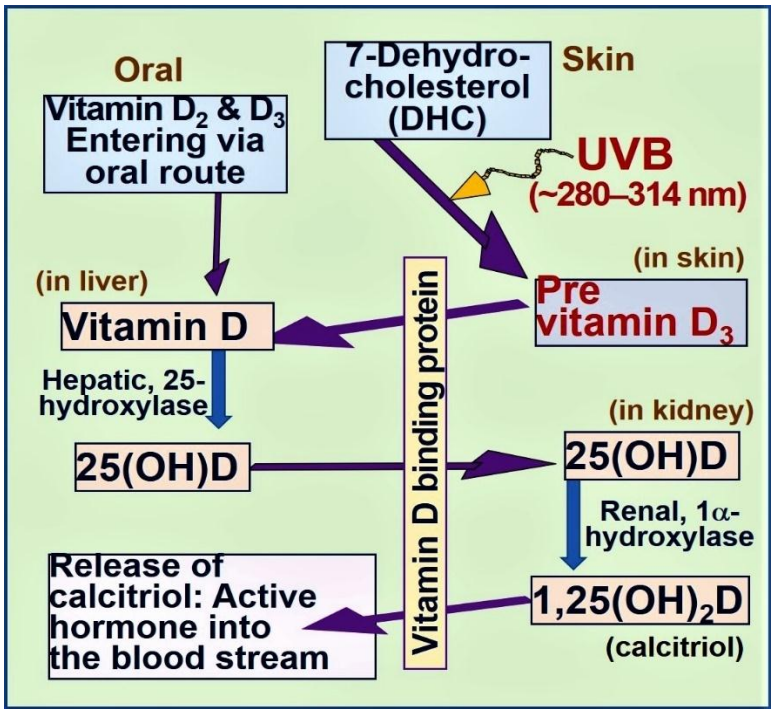

Figure 1: Figure illustrates the activation of metabolic pathways of vitamin D generated in the skin and intake via the oral route. Since vitamin D is a fat-soluble substance, it needs to bind to a carrier, such as vitamin D binding protein for its transportation via the blood stream. It also highlights the three sites, skin, liver and kidneys, where vitamin D is metabolized, stepwise into its activated form, 1,25$(OH)_2$D—calcitriol.

Toxicity from excess vitamin D and its clinical management

Because of inherent feedback protective mechanisms developed through evolution, excessive exposure to sunlight automatically switch the production to inactive metabolites and any excess previtamin D generated will get catabolized within the skin. This prevent excess previtamin D/vitamin D coming into the circulation. Therefore, exposure to sun will not cause hypervitaminosis D. Nevertheless, excessive exposure to UVA and UVB rays can cause DNA and skin damage and thus increase the risk of initiating certain types of skin cancers in genetically susceptible people.

Toxicity from excess vitamin D is extremely rare. Adverse manifestations are exclusively attributable to increased serum ionized calcium (Ca^{2+}) concentration. Therefore, apart from stopping supplements, clinical management is identical to the management of other hypercalcemic conditions. Although the most important step is to maintain proper hydration, symptomatic patients may need temporary dialysis to bring serum ionized calcium concentrations to the upper normal range.

With maintenance of proper hydration and diuresis, most cases of hypercalcemia will resolve, but a few patients might require a short course of calcitonin or an intravenous infusion of a bisphosphonate, such as 4 or 5 mg of zoledronic acid over several hours, to reduce the rate of release of calcium from skeletal tissues through the reduction of bone turnover. No action is needed to reduce the serum vitamin D concentration because the half-lives of both 25(OH)D (2 to 3 weeks) and 1,25$(OH)_2$D (less than 24 hours) are short. In the overwhelming majority of cases, overdosing is caused by accidental ingestion or mistakenly taking high doses of vitamin D.[2]

Blood levels of 25(OH)D needed to maintain good health

The minimum concentration of vitamin D in blood [measured in serum, as 25(OH)D concentration] needed to maintain good health in humans is estimated as 30 ng/mL (75 pmol/L). Although a few think that 20 ng/mL

(50 pmol/L) is adequate, most scientists and physicians consider 30 ng/mL as the minimum concentration necessary to maintain normal physiological functions and good health.[3] Those who are vulnerable to certain diseases, such as cancer, autoimmune disorders, and infections, and those with metabolic disorders are benefitted by maintaining their serum 25(OH)D concentration in excess of 40 ng/mL (100 pmol/L).[4]

Scientific data suggest that keeping individual and population serum 25(OH)D concentrations above 30 ng/mL on a long-term basis[5] significantly reduces morbidities—preventing disease severity and minimizing the acquiring of new disorders,[6] and reduce premature deaths[7] of millions of people across the world. Whereas, other studies have reported that serum 25(OH)D concentrations of less than 20 ng/mL increase insulin resistance and reduce insulin secretion from beta cells in the pancreas,[8] and increase cardiovascular disease[9] and sicknesses.[10] Figure 2 illustrates serum 25(OH)D concentration versus clinical benefits and the threshold.

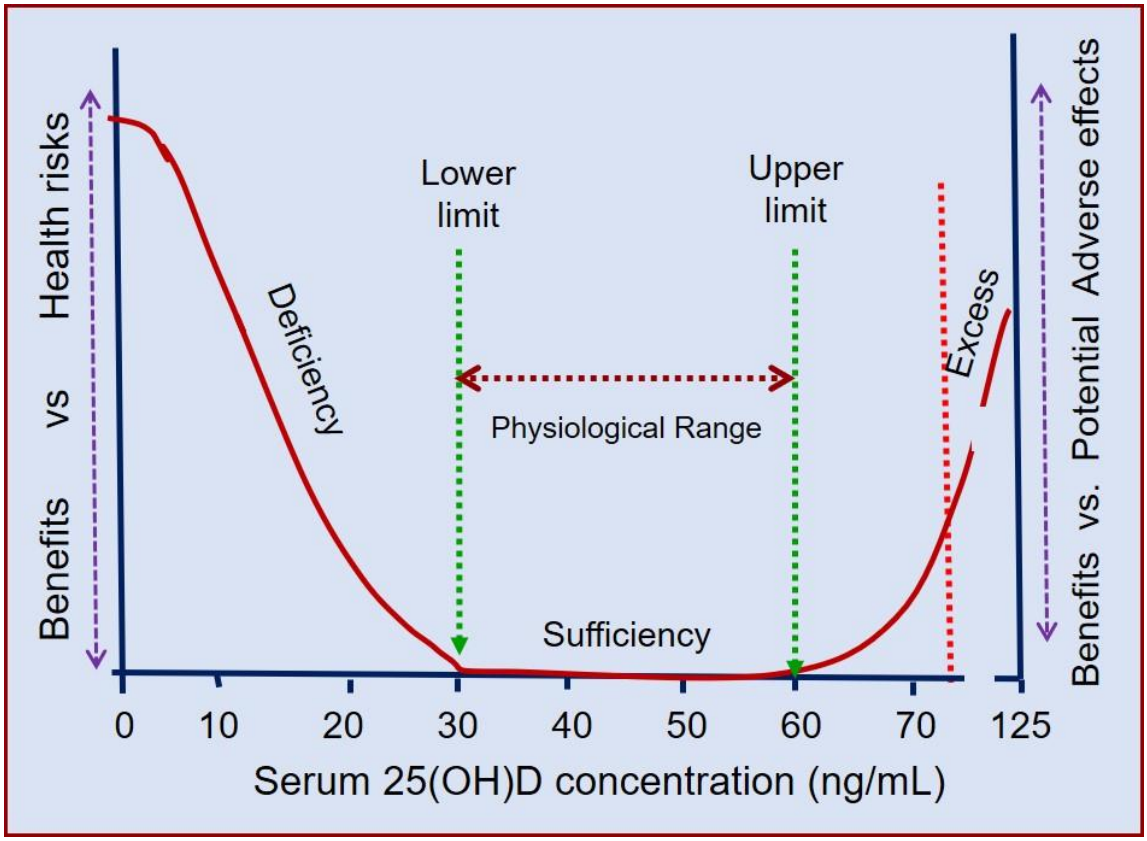

Figure 2: The relationships between serum 25(OH)D concentrations with physiological benefits. The curve also demonstrates the adverse effects associated with two extremes, hypo and hyper vitaminosis D. Conceptual curve was generated from a large number of data from different studies.

Importance of preventing vitamin D deficiency

Despite thousands of research studies supporting the mentioned public health concept and improved clinical outcomes with maintaining serum 25(OH)D concentration above 30 ng/mL, in many countries little action has been taken to rectify to overcome hypovitaminosis D. Politicians and hospital administrators are in general unwilling to take actions to prevent disease, including rectifying population vitamin D deficiency, but are content to spend billions of dollars for expanding acute medical care, building new hospitals and increasing the number of beds. Public health point of view, these actions make no sense. Prevention of diseases is the cure.

The major sociomedical issues in most countries are the escalating incidences of chronic and non-communicable diseases. Nevertheless, delaying or not taking affirmative actions to prevent chronic diseases continues to increase healthcare-associated costs and the sickness pool. One such example is the failure to take a cost-effective approach to alleviating micronutrient deficiencies that aggravate a number of diseases and there by escalating healthcare costs.

In the case of vitamin D deficiency, it not only increases the risk of falls and fractures but also the severity of several common diseases and disorders, including obesity, insulin resistance,[11] type 2 diabetes[9], pregnancy complications[10,12], autoimmune disorders[13], certain cancers[14,15], systemic inflammation[16], and impairment of DNA repair and oxidative stress that potentiate metabolic illnesses, such as cardiovascular disorders[17] and thus premature deaths.[3,18]

How much vitamin D is needed?

Exposure of the skin to UVB rays from sunlight is the main source of vitamin D. Other sources of vitamin D include fatty fish (salmon, herring, tuna, and mackerel), and sun-exposed mushrooms, and oral supplementation. Vitamin D deficiency and insufficiency are common and affect approximately four billion people in the world. Considering that hypovitaminosis D increases the severity of other disorders worldwide, it is estimated to add more than $280 billion in costs to the healthcare system.

Adequate sun exposure of between 15 and 40 minutes each day based on darkness of the skin, in summer-like sunlight or daily intake of a maintenance dose of between 1,000 and 2,000 IU of vitamin D can eliminate the population vitamin D deficiency.[19] However, supplementation should not be given to those with hypercalcemia, hypercalciuria, hypervitaminosis D, and renal osteodystrophy, and hyperphosphatemia, or to those with granulomatous diseases, such as sarcoidosis.

However, those who are at higher risk or have comorbidities[20] or hypovitaminosis D-associated complications, such as those with neurodevelopmental disabilities[21] and pregnant and lactating women[12], may require between 4,000 and 6,000 IU/day (or 50,000 IU every one to two weeks)[18] to maintain optimum physiological effects of vitamin D and prevent complications.[3] These groups and those with obesity and metabolic disorders will have less complications by maintaining their serum 25(OH)D concentrations greater than 40 ng/mL.[22] Although the safe upper limit of daily oral vitamin D intake is considered 6,000 IU[20], daily doses as great as 10,000 IU have been reported to be safe in adults[20,22] [for more information please visit https://vitamindwiki.com/VitaminDWiki].

Drug interactions related to vitamin D

There are few things to be aware of when vitamin D supplements are prescribed. For example, glucocorticoids reduce intestinal calcium absorption and thus, indirectly impairing vitamin D metabolism. The intestinal absorption of all fat-soluble vitamins, including vitamin D, is impaired in the presence of medications and disorders causing fat absorption, such as cholestyramine and orlistat. This can be minimized by taking such medications several hours apart.

Some classes of drugs, such as anti-epileptic agents, including phenobarbital and phenytoin, as well as anti-retroviral drugs increase the hepatic catabolism of vitamin D and generate inactive compounds. With time, this causes functional vitamin D deficiency, which leads to decreased intestinal calcium absorption, development of secondary hyperparathyroidism, and reduced bone mineralization, causing osteomalacia.

Rectifying vitamin D deficiency is easy and highly cost-effective

The treatment of vitamin D deficiency on average costs less than 0.1% (varies between 0.2% and 0.06%) of the cost of investigations and treatment of worsening comorbidities and complications associated with hypovitaminosis D.[23] For example, the cost of vitamin D supplementation to maintain serum 25(OH)D is approximately $12 per person/year, versus an average cost of $6,000 to $18,000/year per affected person to manage vitamin D deficiency-associated diseases and related complications. Despite the high benefits relative to the cost of correcting vitamin D deficiency and maintaining physiological serum 25(OH)D concentrations and the related reduction in comorbidities and complications, millions of people continue to have vitamin D deficiency and unnecessarily get sick.

Most available data support that individual and 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.[3] However, as mentioned, for prevention of certain diseases, such as autoimmune disorders and cancer[24], and to reduce all-cause mortality, it is advisable to maintain serum 25(OH)D concentrations between 40 and 60 ng/mL.[10,25] Doing so requires more sun exposure and/or appropriately higher doses of oral supplementation of basic vitamin D.

None of the activated forms of vitamin D is recommended as supplement for vitamin D deficiency or for osteoporosis. These agents are not only several times more expensive than the ordinary form of vitamin D but also have significant adverse effects. Activated vitamin D is indicated only for those with liver or renal impairment, in whom one of the two hydroxylation steps of vitamin D is impaired.

Some are still reluctant to keep their patient's vitamin D sufficient

Despite the wide availability of the knowledge that hypovitaminosis D is harmful to people, some physicians are reluctant to advise patients of the benefits of vitamin D supplements and safe sun exposure. In the absence of such counsel, patients are experiencing easily preventable medical conditions and metabolic disorders. Other clinicians do not consider or request measurement of serum 25(OH)D concentrations in patients.[26] Other healthcare workers are not aware of or appreciate the beneficial effects of micronutrients, such as vitamins A and D and antioxidants.

For those who are at high risk for deficiency, offering vitamin D supplements is reasonable, but refusal to test serum 25(OH)D in borderline cases is unethical. Despite that testing of vitamin D costs approximately $2 per test, most laboratories continue to charge more than $80 per

test. Because of these high costs of testing, routine testing for vitamin D is not recommended.[20]

Meanwhile, a robust, point of testing method for 25(OH)D must be developed costing less than $1 per test, as in the case with finger-stick measurement of blood sugar. This important technology would overcome the reluctance of physicians to prescribe vitamin D to those who genuinely need such nutrient replacement therapy. It would prevent the unnecessary costing and suffering of those with vitamin D insufficiency and deficiency and minimize complications.

Meanwhile, few scientists and government-appointed committees, such as the Institute of Medicine, United States Preventative Task Force[27], and physician groups, continue to oppose the implementation of highly cost-effective, beneficial, and straightforward public health disease prevention measures that have little or no downside.[28,29] Micronutrient supplementation, such as for iodine (for prevention of goiter), ferrous (iron-deficiency anemia), antioxidants and coenzyme Q10 (for prevention of cardiovascular disease), vitamin A (for preventing keratomalacia and blindness), vitamin C (for preventing scurvy), and B12 (for treating pernicious anemia), when provided to targeted, vulnerable populations, is highly cost-effective in preventing diseases.

Micronutrients and food fortification

Despite mentioned illogical healthcare approaches, employers should seriously consider maintaining vitamin D sufficiency in their employees through their employee health officials. This can be accomplished by encouraging and facilitating employees to receive safe sun exposure (e.g., staggered lunch breaks) and/or the reimbursement of employees for purchasing micronutrient supplements or the provision of supplements through employee health departments. Empowered physicians can advise and prescribe properly, with appropriate amounts of oral vitamin D that cost less than $12/person per year, with or without other essential appropriate micronutrients.

All evidence suggests that micronutrient supplementation, such as food fortification programs, are cost-effective options for alleviating this problem. As mentioned, having physiological concentrations of vitamin D in the blood is known to prevent several common diseases. Thus, it can be considered unethical for healthcare providers to knowingly refuse to address this issue with those in their care. However, as the deficiency status varies from country to country, micronutrient supplementation should be targeted for specific needs [i.e., deficiency status(s)] in a specific country, region, or ethnic group, as appropriate.

For example, food fortification programs should be targeted to fortification of needed micronutrient(s) in food commonly consume by the majority of people in a given population, individually or combined fortification, or through combined micronutrient supplementation with one capsule. There is no one standard formula applicable to all because the requirements vary depending on the population. Currently, raising the population sperm 25(OH)D concentration above 30 ng/mL is perhaps the most cost-effective public health intervention one could implement to prevent acute and chronic illnesses in any given country.

SUMMARY

Despite the publication of more than 40,000 research papers that support multiple beneficial effects of vitamin D, globally, the number of people with vitamin D deficiency continues to increase. However, transferring this wealth of knowledge into action has been hampered by the publication of a handful of poorly designed and conducted, large clinical studies during the past 2 years; these studies provided confusing and contradictory information. Irrespective of the size of these clinical studies and millions of sponsored moneys spent, any clinical studies with inferior study designs generate untrustworthy data.

A population serum 25(OH)D concentration greater than 30 ng/mL is estimated to reduce the health-related and opportunity costs of an average person by approximately $1,500/person/year, which represents a 60-fold, cost–benefit ratio of making the population vitamin D sufficient. In addition, it will keep millions of people healthy, out of hospitals, and in the workforce or schools. Vitamin D sufficiency reduces workplace and school absenteeism and opportunity costs and enhances productivity; a win:win situation.

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