REVIEW ARTICLE

Vitamin D3 Deficiency: Prevalence, Prevention, and Prevailing Management Strategies

SANJAY KALRA*, MADHUR VERMA†, NITIN KAPOOR‡, PRASHANT AGRAWAL#, SAHER KHAN¥

ABSTRACT

Vitamin D is a fat-soluble vitamin and plays a vital role in human physiology. Vitamin D3 deficiency is a significant public health issue globally, with varying prevalence depending on geographic, socioeconomic, and demographic factors. Vitamin D3 deficiency can be influenced by a variety of risk factors that affect its synthesis, absorption, and metabolism. This deficiency has an impact on both musculoskeletal and nonmusculoskeletal health. This article summarizes the prevention and treatment strategies for combating vitamin D3 deficiency, current guidelines for vitamin D supplementation across different age groups, comparative efficacy of oral versus intramuscular vitamin D supplements, and factors influencing response to vitamin D supplementation. The Indian diet frequently lacks adequate levels of vitamin D, owing to its scarcity in commonly consumed foods. This emphasizes the need for fortification of staple foods with vitamin D through national programs. This would ensure that vitamin D reaches even the most underserved populations, including those in rural or low-income settings.

Keywords: Vitamin D, vitamin D3 deficiency, vitamin D3 supplements, food fortification, risk factors, prevention, public health

Vitamin D is an essential micronutrient for maintaining human health, including bone health, immune function, muscle function, cardiovascular health, mental health, regulating inflammation, and cell growth and differentiation[1]. The two primary forms of vitamin D are ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3)[2]. It is primarily synthesized in human skin when exposed to solar ultraviolet-B radiations, whereas only a minor part is derived from dietary sources, such as egg yolk, fatty fish, beef liver, cow milk, and some fortified foods[2]. Vitamin D2 is synthesized from ergosterol and is present in mushrooms and yeast. Deficiency of vitamin D3 significantly impacts musculoskeletal health, causing rickets in children, osteomalacia and osteoporosis in adults, increased bone loss, and muscle weakness. It has also been associated with nonmusculoskeletal conditions, such as increased blood pressure, cardiovascular disease (CVD) risk, diabetes, neoplasia, malignancies, autoimmune diseases, inflammatory bowel disease, and infections like tuberculosis[3]. Therefore, a comprehensive multipronged strategy targeting adequate sun exposure, dietary changes, nutritional supplements, obesity management, special attention to the darker-skinned population, and education is required to combat vitamin D deficiency[4,5].

Therapeutic management of vitamin D3 deficiency includes intake of supplements, which are superior to vitamin D2 due to their higher bioavailability and half-life[6]. While conventional oral fat-soluble vitamin D3 supplements offer simple and cost-effective options, their efficacy is limited due to their lipophilic nature and low gastrointestinal absorption. Newer hydrophilic micellized vitamin D3 formulations have enhanced bioavailability and better therapeutic response but are less preferred due to their comparatively higher cost[7].

Vitamin D deficiency is a major global public health issue, with significant prevalence and treatment disparities across regions and populations[8-10]. However, there is a lack of comprehensive reviews on its global epidemiology and optimal treatment strategies, particularly in the context of diverse populations and geographic

*Treasurer, International Society of Endocrinology (ISE); Vice President, South Asian Obesity Forum (SOF); Bharti Hospital, Karnal, Haryana, India
†Associate Professor, Dept. of Community and Family Medicine, All India Institute of Medical Sciences, Bathinda, Punjab, India
‡Professor and Head (Unit 1), Dept. of Endocrinology, CMC, Vellore, Tamil Nadu, India; Noncommunicable Disease Unit, Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia
#Assistant General Manager, Medical Affairs, Mankind Pharma Ltd., New Delhi, India
¥Assistant Manager, Medical Affairs, Mankind Pharma Ltd., New Delhi, India
Address for correspondence
Dr Madhur Verma
Associate Professor
Dept. of Community and Family Medicine, All India Institute of Medical Sciences, Bathinda, Punjab, India - 151 001
E-mail: drmadhurverma@gmail.com

factors. Therefore, in the current review, we address the global and national prevalence of vitamin D3 deficiency, its risk factors, its impact on health, prevention and management strategies, and efficacy of currently available vitamin D3 supplement formulations.

OPTIMAL LEVELS OF VITAMIN D

The metabolite 25-hydroxyvitamin D [25(OH)D] is the primary circulating form of vitamin D, with an estimated half-life of 2 to 3 weeks and high stability. In contrast, the active form, 1,25-dihydroxyvitamin D [1,25(OH)2D], is chemically unstable and has a half-life of a few hours. Hence, 25(OH)D is used as a standard biomarker to assess vitamin D status[9,11,12]. There exists an inverse relationship between 25(OH)D and parathyroid hormone (PTH) levels; PTH levels tend to increase with a decrease in vitamin D levels. However, PTH is unstable compared to other peptide hormones and breaks down into inactive fragments in the bloodstream after venipuncture. Owing to its instability, specific conditions and protocols must be strictly followed to accurately measure PTH levels[11]. Various societies and health organizations have put forth guidelines for defining optimal levels of vitamin D (Table 1[13-20]).

EPIDEMIOLOGY OF VITAMIN D3 DEFICIENCY

Global Prevalence of Vitamin D3 Deficiency

The status of vitamin D levels varies across the globe owing to geographical, cultural, and environmental differences. People from high-latitude areas have a higher prevalence of vitamin D deficiency than those from lower-latitude areas[10]. The Eastern Mediterranean region and lower-middle-income countries have a higher prevalence[10], while European Caucasians show lower rates of vitamin D deficiency than those in nonwhite individuals[9]. Limited data from representative surveys from individual countries suggest a low overall prevalence of vitamin D deficiency in South America, Oceania, and North America. Severe vitamin D deficiency, defined as 25(OH)D <30 nmol/L, affects 5.9% of the US population, 7.4% of Canadians, and 13% of Europeans. The prevalence of 25(OH)D levels <50 nmol/L is estimated to be 24% in the US, 37% in Canada, and 40% in Europe[9]. There is a more moderate prevalence in Europe, Asia, and Africa[8]. Despite the abundant sunlight in Southeast Asia, 22.0% of the Southeast Asian population have serum 25(OH)D levels <30 nmol/L[10]. More than 20% of the population in India, Pakistan, and Afghanistan have 25(OH)D levels <30 nmol/L[9,21]. Among South Asian countries, the highest prevalence of vitamin D deficiency was found in Pakistan, followed by Bangladesh, India, Nepal, and Sri Lanka[22].

Prevalence of Vitamin D3 Deficiency in India

Vitamin D deficiency affects people of all age groups and backgrounds in India, with an estimated prevalence of 80% to 90%[23]. It has been estimated that 490 million individuals are vitamin D deficient in India[24,25]. The overall

Table 1. Definition of Vitamin D Status According to Different Health Organizations and Societies

Society/Organization	Year	Deficiency	Insufficiency	Sufficiency	Toxicity
Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC[13]	2011	<12 ng/mL (<30 nmol/L)	12 to <20 ng/mL (30 to <50 ng/mL)	≥20 ng/mL (≥50 nmol/L)	>60 ng/mL (>150 nmol/L)
Brazilian Endocrine Society[14]	2014	<20 ng/mL (50 nmol/L)	20-29 ng/mL (50-74 nmol/L)	30 and 100 ng/mL (75-250 nmol/L)	-
Global Consensus Recommendation for Prevention of Rickets[15]	2016	<30 nmol/L	30-50 nmol/L	>50 nmol/L	>250 nmol/L
Institute of Medicine, USA[16]	2018	<12 ng/mL	21-29 ng/mL	>29 ng/mL	-
ICMR-NIN, India[17]	2020	<12 ng/mL	20-29 ng/mL	30-32 ng/mL	-
National Institute of Health Office of Dietary Supplements, USA[18]	2018	<12 ng/mL (>30 nmol/L)	-	>20 ng/mL (>50 nmol/L)	>50 ng/mL (>125 nmol/L)
Indian Academy of Pediatrics[19]	2022	<12 ng/mL	12-20 ng/mL	>20 ng/mL	>100 ng/mL
Endocrine Society Clinical Practice Guideline, USA[20]	2024	Endocrine Society guidelines (2024) no longer specify 25(OH)D optimal values to describe vitamin D sufficiency, insufficiency, and deficiency.			

ICMR = Indian Council of Medical Research, NIN = National Institute of Nutrition.

prevalence of vitamin D deficiency in Indian preschool children (1-4 years), school age (5-9 years) children, and adolescents (10-19 years) during 2016-2018 was 13.7%, 18.2%, and 23.9%, respectively[26,27]. Community-based studies in India on healthy individuals have found prevalence rates ranging from 50% to 94%. Hospital-based studies in India showed a prevalence of vitamin D deficiency ranging from 37% to 99%[23]. The prevalence of 25(OH)D levels <20 ng/mL among Indian women from September 2017 to January 2018 was 64.06%, and that of 25(OH)D levels <30 ng/mL was 98.75%. Additionally, vitamin D deficiency was more prevalent in illiterate women (89.92%), housewives (70%), women residing in rural areas (69.94%), and women having income <10,000 INR (61.96%)[28]. A recent study reported high prevalence of severe vitamin D deficiency among women, obese individuals, and residents in urban areas of Delhi[29].

RISK FACTORS FOR VITAMIN D3 DEFICIENCY

Vitamin D3 deficiency can be influenced by several risk factors, including demographics, age, sex, ethnicity, lifestyle factors, socioeconomic status, pregnancy, lactation, comorbidities, and concomitant medication (Table 2[10,30]).

Demographics

The amount of melanin in the skin affects vitamin D status because the skin depends on ultraviolet rays to synthesize vitamin D, and darker skin inhibits its production. Ames et al[31] reported that people with darker skin at higher latitudes are slower to produce vitamin D and have a higher prevalence of vitamin D deficiencies than lighter-skinned individuals at the same latitudes.

Age and Sex

According to the U.S. Department of Health and Human Services, breastfed infants may be at risk of vitamin D deficiency because human milk has limited vitamin D content. Similarly, older adults are also at risk because their skin does not synthesize vitamin D as efficiently as they age[2]. A recent systematic review by Cui et al[10] showed that females were more vulnerable to vitamin D deficiency than males.

Ethnicity and Lifestyle

African Americans and Hispanic populations have significantly lower levels of vitamin D biomarker 25(OH)D than non-Hispanic whites (white Americans) due to a combination of skin pigmentation and lifestyle factors[32]. People who spend less time outside, work indoors, or live in areas with little sunlight are at risk of vitamin D deficiency.

Vitamin D deficiency can be caused by insufficient dietary consumption, especially among individuals following a strict vegan diet. Excess body weight and obesity are consistently characterized by lower 25(OH)D blood levels and a higher prevalence of vitamin D insufficiency and deficiency in cross-sectional studies[33]. A meta-analysis suggested that the level of circulating 25(OH)D is lower in smokers than in nonsmokers[34]. A hospital-based prospective study indicated that

Table 2. Risk Factors for Vitamin D3 Deficiency Indicating Low- and High-Risk Populations

Risk factors	Low-risk population	High-risk population
Demographics	Individuals with lighter skin, and those who reside in lower latitudes.	Individuals with darker skin, and those who reside in higher altitudes.
Age	Adults (45-64 years) (13.8%)[10]	Breastfed infants (0.6%-91.1%), younger age group (19-44 years) (18.2%), and older adults (>65 years) (15.3%)[10,30].
Gender	Males (13.6%)	Females (17.8%)
Ethnicity/Race	African-Americans	White-Americans
Lifestyle	Physically active individuals, non-smokers	People with strict vegan diets, obese and physically inactive individuals, smokers
Socioeconomic status	Upper-middle-income countries (10.2%)[10]	Lower-middle-income countries (26.7%).
Pregnancy	Nonpregnant women	Pregnant and lactating women.
Comorbidities	Healthy individuals	Individuals with bone diseases, noncommunicable chronic diseases, infectious and communicable acute diseases.
Concomitant medications	Healthy individuals	Individuals on medications

serum vitamin D 25(OH)D levels are significantly higher in physically active individuals than in physically underactive controls[35]. Further, a recent meta-analysis of observational and experimental studies showed a significant positive correlation between physical activity and an individual's serum vitamin D 25(OH)D levels[36].

Socioeconomic Status

Vitamin D insufficiency may be associated with socioeconomic status. People with lower socioeconomic status may have less consumption of vitamin D-rich foods and limited access to routine check-ups and preventive care, leading to undiagnosed or untreated vitamin D deficiency. Within the World Bank income groupings, the prevalence of serum 25(OH)D <30 nmol/L ranged from 10.2% in upper-middle-income countries to 26.7% in lower-middle-income countries. As a result, people in low-income and lower-middle-income nations need greater attention[10].

Pregnancy and Lactation

Pregnant women have reduced outdoor activity or sun exposure due to fatigue and health concerns, which can contribute to lower vitamin D synthesis. During lactation, a woman's body requires additional nutrients to produce breast milk. Vitamin D deficiency among pregnant and lactating women has become a common global problem[37]. Insufficiency or deficiency of vitamin D during pregnancy has a significant impact on the health of pregnant women and pregnancy outcomes, such as gestational diabetes, gestational hypertension, premature rupture of membranes, and premature delivery[38].

Comorbidities

Bone diseases like rickets in children, osteomalacia, and osteoporosis in adults are related to vitamin D insufficiency. Low vitamin D levels may be associated with several noncommunicable chronic diseases, including musculoskeletal disorders, obesity, type 1 and type 2 diabetes, polycystic ovary syndrome, male hypogonadism, cancer, dementia, autism, inflammatory bowel disease, rheumatoid arthritis, CVD, and renal and liver disease[39,40]. Vitamin D has a significant role in the clinical course of infectious and other communicable acute diseases, particularly respiratory bacterial infections, tuberculosis, and virus infections, such as those caused by human immunodeficiency (HIV) and SARS-CoV-2 (COVID-19) viruses. Low vitamin D levels are also related to an increased risk of falls, fractures, muscle pain, muscle weakness, infections, and autoimmune disorders[23,41].

Concomitant Medication

Polypharmacy, the concurrent use of multiple medications in older adults, can be a significant risk factor for vitamin D deficiency[42]. Several groups of drugs have been found to affect vitamin D levels, including antidiabetic, cardiovascular, gastrointestinal, anti-inflammatory, and central nervous system medications, enzyme-inducing antiepileptic drugs, antimicrobials, antiretroviral agents, and specific chemotherapeutic agents.

IMPLICATIONS OF VITAMIN D3 DEFICIENCY

Impact on Musculoskeletal Health

Vitamin D is crucial for calcium and phosphorous absorption and bone mineralization, essential for healthy skeletal growth. Infants need more vitamin D owing to their rapid skeletal growth and development. During the first 4 months of life, an infant's diet primarily consists of breastmilk or infant formula. Breastmilk is a natural source of nutrients, including vitamin D, but the concentration of vitamin D in breastmilk is low and ranges from 25 to 124 IU/L[43]. Most international guidelines recommend that breastfed infants receive a daily vitamin D3 supplement of 400 IU during the first year of life[30]. Fractures of the wrist, hip, and vertebrae are the three main manifestations of osteoporosis and, in high-risk populations (older adults), cause excess mortality, considerable economic burden, and decrease in quality of life[44]. As serum 25(OH)D levels decrease with age, increased supplementation is necessary for most older individuals. According to a systematic review and meta-analysis of 6 randomized clinical trials, daily supplementation of both vitamin D (400-800 IU) and calcium (1,000-1,200 mg) is associated with a 16% reduced risk of hip fracture in older adults[45].

Vitamin D levels also affect muscle strength, muscle size, and neuromuscular performance. With increasing age, muscle mass loss is associated with lower circulating vitamin D levels, leading to frailty in the elderly and frequent falls[46]. Vitamin D deficiency has been implicated as a potential factor contributing to sarcopenia, which is the progressive loss of muscle mass and strength that occurs with aging. A meta-analysis of 47 randomized controlled trials recommended daily vitamin D3 supplementation with ≥800 IU combined with calcium to prevent falls and fractures[47].

Impact on Nonmusculoskeletal Health

Vitamin D deficiency significantly affects various body systems like the immune system, cardiovascular system, mental health, cancer, chronic diseases, metabolic health,

acute respiratory infections, autoimmune diseases, neurological function, pregnancy, and neonatal health. The expression of the vitamin D receptor and metabolizing hormone in a range of immune cells, including lymphocytes, monocytes, macrophages, and dendritic cells, indicates the role of vitamin D in both innate and adaptive immune systems[48,49]. Several studies suggest a close association between low vitamin D levels and major CVDs, such as heart failure, coronary artery disease, and atrial fibrillation[50-53]. Increased PTH levels in blood, frequent among persons with vitamin D deficiency, have been shown to contribute to advancing CVD[54]. Further, low vitamin D levels are associated with increased symptoms of mental health disorders (depression, anxiety, and stress)[55-57].

Long-term vitamin D insufficiency can lead to major acute and chronic diseases, such as type 1 and type 2 diabetes[58], cancer[59,60], autoimmune diseases[3,61-63], and liver and renal disease[64,65]. Low vitamin D levels are associated with metabolic syndrome[66,67], neurological disorders[67,68], and risk of chronic respiratory diseases, including asthma, cystic fibrosis, and chronic obstructive pulmonary disease[69-71]. A meta-analysis and systematic review of randomized controlled trials showed an association between vitamin D deficiency and an increased risk of respiratory infection from influenza and *Mycobacterium tuberculosis*[72,73]. Further, a recent meta-analysis of 43 observational investigations suggests that low vitamin D levels increased susceptibility, fatalities, and severity of COVID-19 infection[74].

PREVENTION AND MANAGEMENT OF VITAMIN D3 DEFICIENCY

Prevention of Vitamin D3 Deficiency

Vitamin D3 deficiency is often ignored in outpatient and inpatient settings. The United States Preventive Services Task Force (USPSTF) does not advise universal vitamin D screening; nevertheless, screening for vitamin D deficiency in asymptomatic high-risk groups is critical to prevent its sequelae[75]. High-risk groups include older patients, nursing home residents, women with osteoporosis, African-American/Hispanic individuals, hospitalized patients, patients with chronic renal and liver disease, and patients with malabsorption disorder[76].

Increasing vitamin D awareness through public education efforts can help prevent long-term health concerns. The strategies described below, including dietary changes, lifestyle interventions, obesity management, and food fortification, ensure a comprehensive approach to prevent vitamin D deficiency.

Dietary and lifestyle interventions

Vitamin D can be obtained from egg yolk, salmon, canned tuna, cod liver oil, beef liver, mushrooms, and vitamin D fortified sources[2]. A cross-sectional observational study by Barrea et al[77] indicated that strict adherence to the Mediterranean diet increased 25(OH)D levels among adults. Further, moderate sun exposure (5-30 min) without sunscreen for short periods, several times a week, can help the body produce vitamin D naturally[78]. Endurance exercises, such as prolonged outdoor activities or consistent training, can increase serum 25(OH)D levels in vitamin D-deficient individuals[79,80].

Thirty minutes of sunshine daily can help prevent vitamin D deficiency[81]. Although sunlight exposure is a natural and effective way for the body to produce vitamin D, it is insufficient to prevent deficiency. Vitamin D supplementation is needed for prevention, particularly in high-risk individuals. The daily allowance of vitamin D through life stages recommended by different health organizations to prevent vitamin D deficiency is presented in Table 3[82].

Table 3. Vitamin D Recommended Daily Allowance for Various Life Stages, According to Different Organizations

Life stages	Institute of Medicine (2011)[13]	Endocrine Society (2024)[20]	ICMR, NIN (2020)[17]	FSSAI (2019)[83]
0-12 months	400 IU/day	400 IU/day	400 IU/day	400 IU/day
1-18 years	600 IU/day	*Empiric vitamin D supplementation	600 IU/day	400-600 IU/day
19-70 years	600 IU/day	600 IU/day	600 IU/day	400-600 IU/day
>70 years	800 IU/day	*Empiric vitamin D supplementation	600 IU/day	800 IU/day
Pregnant and lactating women	600 IU/day	*Empiric vitamin D supplementation	600 IU/day	-

*Empiric vitamin D supplementation [vitamin D consumption that exceeds IOM's RDA and is implemented without testing for 25(OH)D].

FSSAI = Food Safety and Standards Authority of India; IOM = Institute of Medicine; RDA = Recommended Daily Allowance.

Food fortification

Vitamin D dietary fortification is an effective approach for improving vitamin D status, and it has already been implemented by countries such as Canada, USA, India, and Finland[84,85]. In contrast to Western countries, where milk, dairy products, and cereals are fortified with vitamin D, Asian countries have few vitamin D-fortified foods[86]. In 2018, the Food Safety and Standards Authority of India (FSSAI) operationalized the Food Safety and Standards (Fortification of Foods) Regulations, 2018 for fortifying milk (with vitamin D, 5-7.5 µg/L of milk) and edible oil (with vitamin D, 0.11-0.16 µg/gm of oil) to reduce the burden of micronutrient malnutrition in India[83]. Traditional Indian diets are primarily composed of cereals and lack vitamin D-fortified foods. Therefore, fortifying commonly consumed staple foods such as rice and wheat will ensure a broader reach across different socioeconomic Indian populations and is a strategic approach for combating vitamin D deficiency in India[86,87].

Management of Vitamin D3 Deficiency

Vitamin D supplements

Sunlight exposure and dietary consumption are typically insufficient to maintain optimal vitamin D status, and vitamin D supplementation is frequently necessary. The two primary forms of vitamin D supplementation are vitamin D2 and D3. A meta-analysis of 20 comparative studies showed that vitamin D3 is superior to vitamin D2 in terms of bioavailability and raising serum 25(OH)D concentrations[88]. Vitamin D3 supplements are available in various formulations (tablets, capsules, sachets, and oral drops) and strength in India (Table 4). Patil et al[89] found oral chewable tablets to be more effective than capsules and granules in raising serum 25(OH)D levels among individuals with vitamin D deficiency. A recent post-hoc analysis indicated that vitamin D3 supplements in tablets and oil drops are equally effective in raising serum 25(OH)D concentrations[90].

Dosing regimen and duration of therapy

The required dosage of vitamin D supplements depends on several factors including patient age, body weight, absorption issues, baseline levels, sun exposure, diet, bone health, severity of the deficiency, and underlying comorbidities. A randomized clinical study by Munjal et al[91] indicated that a single loading dose (60,000 IU cholecalciferol) of all three oral formulations (liquid, sachet, and tablet) administered to adults with mild vitamin D deficiency significantly increased 25(OH)D serum levels. In vitamin D deficient individuals, vitamin D3 supplementation for the first 8 weeks, at 6,000 IU daily or 50,000 IU weekly, is recommended[76]. Once the serum 25(OH)D level exceeds 30 ng/mL, a daily maintenance dose of 1,000 to 2,000 IU is recommended. However, the upper limits of vitamin D intake must be considered to avoid toxicity. The tolerable upper limit of vitamin D for infants, children, and adults is 1,000-1,500 IU/day, 2,500-3,000 IU/day, and 4,000 IU/day, respectively[18]. A meta-analysis of 116 randomized clinical trials suggests that intermittent and daily supplementation of vitamin D have similar efficacy[92]. However, for treating or preventing tuberculosis, rickets, and acute respiratory infections, daily vitamin D supplementation is more effective than intermittent high-dose boluses[93].

Table 4. Vitamin D Formulations Available in India

Various formulations	Form of vitamin D	Strength
Capsule	Cholecalciferol	60,000 IU, 0.25 mg
Capsule	Calcitriol	0.25 µg
Capsule	Alfacalcidol	0.25 µg
Tablet	Cholecalciferol	60,000 IU, 2,000 IU, 1,000 IU
Tablet	Calcitriol	0.25 µg
Sachet	Cholecalciferol	60,000 IU
Syrup	Cholecalciferol	200 IU
Oral solution	Cholecalciferol	60,000 IU, 400 IU
Injection	Cholecalciferol	6,00,000 IU

Vitamin D is crucial during pregnancy and lactation, supporting maternal health and fetal development[37]. The need for vitamin D can vary throughout the trimesters, and supplementation is often considered to ensure adequate levels. The supplementation of vitamin D in the first trimester reduces the risk of pregnancy complications, such as pre-eclampsia and miscarriage. A published Cochrane review suggests that vitamin D supplementation during the second and third trimesters may reduce gestational diabetes, low birthweight, and preterm birth[94]. Considering guidelines provided by various health organizations, daily supplementation of at least 400-600 IU/day is recommended for pregnant women to prevent complications[9].

Comparison of efficacy of oral versus intramuscular vitamin D formulations

Vitamin D supplements can be administered in several forms, i.e., orally (tablets, capsules, chewable tablets or

gummies, and liquid drops) or as intramuscular injection. Few clinical studies have compared the effect of oral and intramuscular vitamin D supplementation on serum 25(OH)D response, and the results are mixed. A prospective interventional study on adults with hip fracture and vitamin D deficiency demonstrated that intramuscular administration is more effective than oral supplements for increasing serum 25(OH)D levels[95]. A randomized clinical trial among vitamin D deficient patients indicated that all three routes of vitamin D supplement administration (oral, injectable formulation given orally, and intramuscular injection) are equally effective in raising serum 25(OH)D levels, with no significant advantage over one another[96]. Further, a prospective randomized clinical study of 40 healthy adults with vitamin D deficiency showed that equivalent doses of oral cholecalciferol (60,000 IU weekly for 5 weeks) and intramuscular cholecalciferol (3,00,000 IU) are equally effective in correcting vitamin D deficiency[97]. However, Al-Hilali et al[98] observed that vitamin D supplements, when administered intramuscularly, were more effective than oral supplements in raising the required 25(OH)D serum level in adults with hypovitaminosis D.

FACTORS INFLUENCING RESPONSE TO VITAMIN D THERAPY

Several biological and demographic factors, including body mass index (BMI), obesity, genetic factors, dietary fat content, estrogen usage, baseline 25(OH)D status, vitamin D formulation, and dosage, affect vitamin D supplementation efficacy (Fig. 1). Tobias et al[33] found that a higher BMI may be associated with a diminished response to vitamin D supplementation. The blunted response in obese individuals is attributed to lower bioavailability of vitamin D due to sequestration in fat tissue and reduced bioactivity (suppressed hepatic enzyme 25-hydroxylation of vitamin D to 25(OH)D)[99]. Genetic factors, i.e., polymorphisms in some essential genes, including vitamin D receptor and vitamin D binding protein gene of vitamin D metabolic pathways in healthy adults, substantially impact the response to vitamin D supplementation[100].

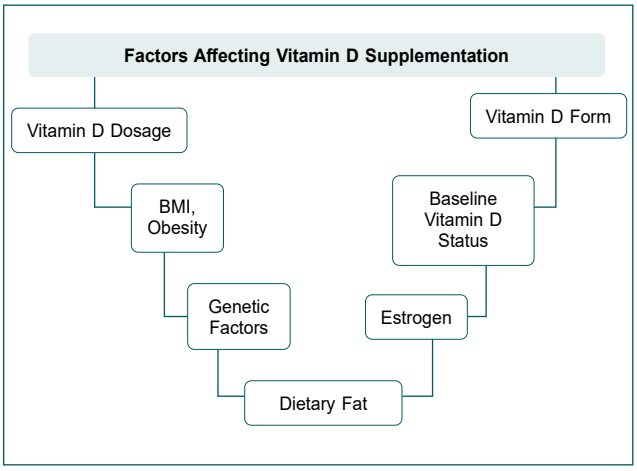

Figure 1. Factors influencing response to vitamin D therapy (adapted from Stokes et al 2016).

A prospective randomized controlled trial demonstrated that estrogen-containing oral contraceptives are associated with increased serum 25(OH)D in response to vitamin D supplementation in premenopausal women[101]. An individual's baseline 25(OH)D concentration also significantly influences the response to vitamin D supplementation[102]. Consuming a vitamin D3 supplement with a meal containing fat may significantly increase absorption of the supplement[103,104]. Additionally, compared with vitamin D2, a vitamin D3 supplement increases serum 25(OH)D levels to a greater extent and maintains these higher levels for longer[88,105]. Appropriate supplement dosage is essential to replenish serum 25(OH)D levels in individuals with vitamin D deficiency. Singh et al[106] found that a higher dose of vitamin D3 (60,000 IU weekly) replenished 25(OH)D levels more rapidly than a 1,000 IU daily dose.

FUTURE DIRECTIONS FOR VITAMIN D SUPPLEMENTATION

Different societies and health organizations have recommended the optimal dosage and duration of vitamin D3 supplements for various age groups. However, clinical trials remain necessary to establish the optimal dosage and duration of vitamin D3 supplementation for different populations, ethnicities, and comorbidities. Studying vitamin D pharmacogenomics can help understand the impact of vitamin D-related gene polymorphisms and epigenetic modifications on interindividual differences in response to vitamin D supplementation[107-109]. Based on these insights, physicians can tailor vitamin D supplementation strategies to ensure optimal levels, especially in individuals genetically predisposed to lower responses to standard supplementation doses. This personalized approach could be critical in managing conditions like osteoporosis, CVD, or autoimmune disorders. Further, a lack of awareness among general and high-risk populations is a primary challenge in vitamin D3 supplementation. Thus, there is a need for educational interventions to enhance awareness regarding vitamin D3 (benefits, deficiency, toxicity, and resources) among these populations. Moreover, the high cost of vitamin D3 supplements limits their use for effective treatment

of vitamin D deficiency. Encouraging cost-effective alternatives, like fortified foods, can help improve vitamin D status in populations that cannot afford supplements.

CONCLUSIONS

Vitamin D3 is crucial for bone health, musculoskeletal and nonmusculoskeletal health, immune function, and prevention of chronic diseases. Vitamin D3 deficiency is a global health issue affecting people in both developed and developing countries. Its management depends on its severity, underlying cause, and individual risk factors. Lifestyle modifications, dietary changes, and fortified foods are often sufficient to treat mild deficiency, while moderate to severe deficiency requires vitamin D supplementation under medical supervision.

Vitamin D supplementation can be administered through various forms, including oral routes (tablets, capsules, chewable tablets, gummies, and liquid drops) and intramuscular injections. Clinical studies comparing the efficacy of oral and intramuscular vitamin D supplementation have produced mixed results, with some studies favoring one method over the other, while others found no significant difference. The response to vitamin D supplementation depends on a complex interplay of biological and demographic factors, including baseline vitamin D levels, form and dosage, BMI, obesity, dietary fat, and genetic factors. Tailoring supplementation strategies to individual needs can help optimize vitamin D levels and improve overall health outcomes.

Declaration of Interest

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Compliance with Ethics

This article involves a review of the literature and did not involve any studies with human or animal subjects performed by any of the authors.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the writing of this article.

Authorship

The named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

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