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ORIGINAL RESEARCH

Prevention and Treatment of Vitamin D Deficiency

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Abstract Vitamin D insufficiency and deficiency are widespread in many countries. We review the evidence pertaining to its prevention and treatment. Deficiency may be adequately treated with many different therapeutic regimens of either cholecalciferol or ergocalciferol, owing to the high therapeutic index of both compounds. Nevertheless, the current evidence suggests that regular dosing with oral cholecalciferol (e.g., 60,000 IU weekly) may have slight advantages over other regimens when replenishing vitamin D stores following deficiency. For long-term supplementation, smaller regular doses, such as cholecalciferol 1,000 IU daily, or 10,000 IU weekly, are suitable. Giving reliable and specific advice about appropriate sunlight exposure remains difficult because of differing interindividual skin pigmentation and variable sunlight UVB content at different latitudes, at different times of year, and in different terrestrial environments.

Keywords Vitamin D · Rickets · Osteomalacia

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Introduction

Despite vitamin D being freely available through UVB sunlight exposure of exposed skin and, to a lesser degree, through eating oily fish, vitamin D deficiency is widespread in many developed and developing countries. This topic consequently figures prominently in a rapidly growing scientific literature as well as in the popular press. This focus is appropriate and reflects the many uncertainties about vitamin D status, particularly its emerging role in extraskeletal health as well as its better-understood relationship to musculoskeletal disease. This article reviews current treatment regimens available for people with vitamin D deficiency and looks at ways of maintaining an adequate vitamin D status in the population as a whole.

Assessing Vitamin D Status

Serum 25-hydroxyvitamin D (25[OH]D) concentration is the best marker of bodily vitamin D status, with a circulating half-life of around 3 weeks. Serum 1,25-hydroxyvitamin D (1,25[OH]D), the active vitamin D hormone, should not be measured as it has a short circulating half-life and does not reflect body vitamin D status [1–5]. Both adults and children with symptomatic vitamin D deficiency (rickets, myopathy, musculoskeletal pain) generally have serum 25(OH)D levels < 30 nmol/L. What constitutes an optimum level of serum 25(OH)D remains uncertain and is different depending on whether skeletal or nonskeletal outcomes are being considered and may also be different at different stages of life. Many authorities are now recommending a serum 25(OH)D concentration of 75 nmol/L or more [6, 7], largely based on evidence from physiological analysis of peak intestinal calcium absorption [8] and an association with

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better health outcomes in large epidemiological studies. Histomorphometric analysis of iliac crest biopsies from 675 individuals demonstrated that pathological mineralization defects only occurred in the context of serum 25(OH)D < 75 nmol/L [9]. Furthermore, studies using serum parathyroid hormone (PTH) response as an index of serum 25(OH)D have recommended wide ranges varying from 30 to 100 nmol/L [10, 11]. Nevertheless, a serum 25(OH)D level of 50 nmol/L or more can also be viewed as adequate for skeletal health [12–15] as there is currently no level 1 (randomized control trial) evidence that supports an improvement in health from elevating 25(OH)D levels from 50 to 75 nmol/L.

There are several different assays available for measuring 25(OH)D concentrations; it is now accepted that liquid chromatography tandem mass spectroscopy is the gold standard. The National Institute of Standards and Technology, in collaboration with the National Institutes of Health's Office of Dietary Supplements, has developed a standard reference material for the determination of 25(OH)D in serum [16–19]. Rigorous use of this standard should improve the assessment, interpretation, and generalizability of serum 25(OH)D levels. This topic is discussed in detail by Fraser (see this issue).

Sources of Vitamin D and Risks for Insufficiency/Deficiency

Can Sunshine Alone Fulfill Our Vitamin D Requirements?

Exposure to solar UVB rays leads to the conversion of 7-dehydrocholesterol to previtamin D_3 in the epidermis. This simple yet critical process is believed to have driven evolutionary changes in skin pigmentation in early human populations as they migrated from Africa [20]. Skin pigmentation therefore modulates the cutaneous synthesis of vitamin D along with the solar zenith angle, which depends on latitude, season, and time of day. As the latitude increases, the UVB rays decrease. This is because during winter months the earth gyroscopically tilts away from the sun. Consequently, the sun's UVB rays traverse a longer oblique distance to reach regions with higher latitudes, with a resultant increase in scatter and absorption of UVB by the ozone and other atmospheric layers.

With regard to pigmentation, some exceptions to the general pattern exist, such as the Greenland Inuit population, who have unexpectedly darkly pigmented skin despite living in Greenland (72°N). They have traditionally subsisted on a diet rich in marine mammals and fish, both rich supplies of vitamin D. With modernization, Inuits surviving on supermarket food suffer from the world's highest prevalence of vitamin D deficiency [20]. With global migration and changes in diet toward processed food over the past century, millions of other people are now at risk of vitamin D deficiency as well [21].

A prospective study conducted in Manchester, UK (53°N), examined whether personal sunlight exposure levels could provide sufficient vitamin D (25[OH]D ≥ 50 nmol/L) in white adults. This not only confirmed that vitamin D synthesis was negligible during the winter months in the United Kingdom but also determined that attaining a peak late summer 25(OH)D level of approximately 80 nmol/L was required to ensure a trough winter level of at least 50 nmol/L [17]; 72 % of the population did not attain the peak level of 80 nmol/L [22]. The same group also examined similar UVB and 25(OH)D dose responses in south Asians and found that all participants had vitamin D levels <50 nmol/L during the winter trough [23]. This indicates that south Asians cannot rely on solar vitamin D production to maintain an optimal vitamin D status in northern latitudes. There were similar findings in African American children living in Texas, USA (32°N) [24]. It, therefore, seems unlikely that dark-skinned people or the majority of fair-skinned people living in northern latitudes will be able to maintain adequate vitamin D levels throughout the year if current population habits with relation to sun exposure go unchanged.

It is of note that public health recommendations and skin cancer–awareness groups have recommended limiting sun exposure over the last 10–15 years to reduce the risk of skin cancers. Public health information that is appropriate in areas such as Australia and Florida (e.g., Sunsmart, Sunsafe) has been disseminated in much more northerly regions, resulting in mixed public health messages [25]. Recently, a U.K. consensus vitamin D position statement advised little and frequent sun exposure (without burning) in order to aid endogenous vitamin D production but also cautioned against a "one size fits all" approach [26]. Importantly, there are significant differences in UVB exposure depending upon whether the skin surface is exposed horizontally to the sun in an unshaded place, such as on a beach, or vertically in a partially shaded urban environment [27]. This, along with interindividual variations in skin pigmentation, makes it very difficult to make widely applicable recommendations, although the general principle of encouraging regular, short-duration exposure remains sound.

Can Natural Dietary Sources Fulfill Our Dietary Requirement?

If sunlight cannot be relied upon to provide adequate vitamin D requirements in the United Kingdom and more northerly latitudes, then an important question is whether

normal food intake is a realistic alternative source. Only a relatively small number of foods contain substantial amounts of vitamin D, the richest dietary sources being oily fish and cod liver oil. The trend toward eating more processed foods means that consumption of fish has declined over many years. In addition, modern methods of intensive aquaculture mean that the "farmed" fish that is commonly consumed has less vitamin D content than wild fish [28]. At least two 150 g portions of oily fish weekly are recommended to achieve adequate vitamin D intake. However, this assumption is based on historical data for fish vitamin D content [29], and there is also likely to be some seasonal variation in this. Food-supplementation policies differ considerably between countries, and milk is widely fortified in several countries, including the United States and Canada. However, in the United Kingdom only infant formula milk and margarine have statutory vitamin D supplementation. Thus, the prevalent U.K. diet, and most probably that in many other European countries, is profoundly lacking in vitamin D, mean daily intakes of 2.8 and 3.7 μg (112 and 150 IU) being recorded for adult U.K. women and men, respectively [30]. This low dietary vitamin D intake combined with the lack of cutaneous production for half of the year explains the disturbingly high prevalence of vitamin D insufficiency across the United Kingdom [31] and in many other European countries.

Who Is at Risk for Vitamin D Deficiency?

As alluded to above, at northern latitudes the major risk factor for vitamin D deficiency at all ages is pigmented skin. This is also the key risk factor in sunnier climates such as Australia, India, and the Middle East, where vitamin D deficiency has also been widely reported [32–34]. Elderly and institutionalized individuals are also at risk because of the relatively large amount of time spent indoors.

Individuals with malabsorption, short bowel, or renal and liver disease; survivors of cancer; and those taking anticonvulsants, rifampicin, or highly active antiretroviral drugs are also at higher risk. Vegetarians, people with photosensitive skin disorders, and those with agoraphobia are also at high risk. Obesity is a risk factor for low serum 25(OH)D, although total-body fat vitamin D stores may be higher, so the clinical significance of the biochemical finding is currently uncertain [35].

Neonatal status is entirely dependent upon maternal vitamin D status, so neonates are frequently deficient at birth. Multiparity, short spacing between pregnancies, and dark maternal skin color are major risk factors [36, 37]. Infants exclusively breast-fed, particularly beyond 6 months of age, are at increased risk because the vitamin D content of breast milk will not meet the requirements of the rapidly growing skeleton [37]. Delayed introduction of solid food, picky eating habits, and poor diet also contribute.

Treating Deficiency

Patients with serum 25(OH)D levels of <25 nmol/L should be considered as severely vitamin D–deficient, as should those with typical symptoms (rickets, osteomalacia, bone pain, hypocalcemia, and myopathy) from high-risk groups who have 25(OH)D levels in the 25–35 nmol/L range [15]. In adult patients, treatment must take into account the fact that the combination of skin synthesis and dietary intake must have been insufficient for years. The general plan of treatment is to replenish stores with a period of pharmacological high-dose cholecalciferol or ergocalciferol therapy to ensure serum 25(OH)D > 50 nmol/L, followed by long-term supplementation (Table 4). There are common areas of uncertainty regarding the role of different treatment formulations, dosing regimens, and routes of administration when treating vitamin D deficiency; and we will address these below based on the available evidence and our own experiences.

Which Is the Most Appropriate Vitamin D Preparation, Ergocalciferol or Cholecalciferol?

Vitamin D may be replaced as either ergocalciferol (D_2) or cholecalciferol (D_3). Whereas ergocalciferol is derived from UV-irradiated ergosterol of fungus or yeast origin, cholecalciferol is animal-derived. It is formed endogenously in the skin of mammals from its prohormone, 7-dehydrocholesterol, following UVB radiation. However, in our natural food chain, the richest source is oily fish, the ultimate source being synthesis in marine zooplankton.

For many years it had been assumed that vitamins D_2 and D_3 are equally bioactive in humans. However, studies in other mammals suggested that this may not be the case [38].

This issue is complicated by the fact that immunoassays for serum 25(OH)D may underestimate the concentration of D_2-derived 25(OH)D. Furthermore, it is clear that ergocalciferol is bound less well by plasma vitamin D binding protein and cleared more quickly from the circulation [39]. Over the past decade, several studies in humans have investigated the bioactivity of these two vitamin D precursors, with conflicting outcomes (Table 1). However, most of the prospective, randomized control trials used serum 25(OH)D as the primary outcome, rather than antirachitic activity. This analysis, therefore, does not necessarily correlate with clinical outcome and may be

Table 1 D_2 vs. D_3

Reference	Objective	Study population	Study design	Conclusion
Binkley et al. [40]	D_2 vs. D_3 1,600 IU daily vs. 50,000 IU monthly	64 adults (>65 years) outpatients	RCT	D_3 slightly but significantly more effective than D_2 in increasing serum 25(OH)D levels; neither regimen ensures >75 nmol/L in all people; no toxicity observed
Cipriani et al. [59]	Single 600,000 IU oral	48 young subjects (36 years)	Prospective interventional study	Single oral high dose of D_3 rapidly improves 25(OH)D levels and reduces PTH
Rapuri et al. [46]	D_2 vs. D_3 vs. controls (401 vs. 465 IU)	418 elderly woman (65–77 years)	Cross-sectional	Both contribute equally to serum 25(OH)D levels
Heaney et al. [41]	D_2 vs. D_3 (50,000 IU/week)	33 healthy adults (49.5 years)	RCT	D_3 87 % more potent than D_2 in raising and maintaining serum 25(OH)D levels
Shakiba et al. [51]	200 vs. 400 vs. 50,000 IU 2-monthly of D_3	120 breast-fed infants	RCT	Bolus dose superior; baseline 25(OH)D levels not available
Siafarikas et al. [61]	250 vs. 500 IU of D_3	40 breast-fed infants	RCT	Both doses provide optimal levels
Thacher et al. [45]	D_2 vs. D_3 (50,000 IU)	17 Nigerian children (2–10 years) with nutritional rickets	RCT	Similar increases in D_2 and D_3 but no effect on fractional calcium absorption
Armas et al. [43]	D_2 vs. D_3 vs. placebo (50,000 IU)	30 healthy men (20–61 years)	RCT	Reduced potency of D_2
Trang et al. [39]	D_2 vs. D_3 (4,000 IU)	34 healthy adults (38 ± 9 years)	RCT	D_2 less efficacious

A meta-analysis by Tripkovic et al. [49] discussed this in detail

RCT randomized, controlled trial

confounded by differences in assay sensitivity. Whereas most studies indicate that cholecalciferol is more potent [39–43], some have suggested that they have similar bioequivalence [44–47].

Holick et al. [44] used doses of 1,000 IU vitamins D_2 and D_3 daily and reported equivalence in raising serum 25(OH)D. These results are consistent with two other studies by Rapuri et al. [46] and Markestad et al. [47]. However, three studies [39, 41, 42], using much higher doses (4,000 IU daily, 50,000 IU/week, and a single dose of 300,000 IU, respectively), reported that vitamin D_3 was more potent than vitamin D_2 at raising serum 25(OH)D. Some authors [41, 43, 48] have even reported a reduction in 25(OH)D levels during vitamin D_2 therapy, although this has not been a consistent finding [44, 45]. High doses of ergocalciferol may upregulate 24-hydroxylase enzymes, leading to more rapid clearance of both exogenous D_2 and endogenous D_3 compounds; and this may explain the differences between lower- and higher-dose studies. Importantly, Heaney and colleagues [41] have recently documented that ergocalciferol was less effective at raising fat calciferol content than cholecalciferol, although relatively small numbers were studied. Finally, a recent meta-analysis by Tripkovic et al. [49] indicated that D_3 is more efficacious than D_2 at raising serum 25(OH)D levels. When the frequency of dosage administration was compared, there was a more pronounced response with vitamin D_3 when given as a bolus dose ($p = 0.0002$) compared with administration of vitamin D_2; but the effect was lost with daily supplementation.

Undoubtedly, there are differences in serum 25(OH)D response to similar doses of calciferols, which is consistent with both analytical and biological variability [40]. To summarize, although both ergocalciferol and cholecalciferol are effective at treating vitamin D deficiency, current evidence suggests that cholecalciferol may have modest advantages in terms of greater duration of action, especially when administered as a bolus. However, a proportion of patients, particularly vegetarians, prefer to take ergocalciferol; and this remains an excellent second choice. Nonetheless, it is also important to clarify that some commercially available cholecalciferol preparations are derived from lanolin in sheared wool and, therefore, are acceptable to the majority of vegetarians.

What Are the Optimal Dose and Dosing Interval for Treating Deficiency?

Both cholecalciferol and ergocalciferol have a high therapeutic index, meaning that large doses can be administered with little chance of toxicity, particularly to

individuals with biochemically documented vitamin D deficiency. Most cases of hypercalcemic vitamin D toxicity are associated with serum 25(OH)D levels in excess of 400 nmol/L, and such levels are difficult to achieve using these conventional calciferol preparations. The exception to this is patients with granulomatous disorders, most commonly either active tuberculosis or sarcoidosis, in whom there is a genuine risk of hypercalcemia on account of 1α-hydroxylation to active vitamin D in granulomatous tissues. Similarly, activated vitamin D analogues (calcitriol or calcidiol/alfacalcidol) should not be used to treat vitamin D deficiency as there is a high chance of toxicity and they are ineffective at replenishing bodily stores.

Owing to the high therapeutic index, there are multiple effective dosing regimens for the treatment of vitamin D deficiency. The immediate aim of treatment is to replenish vitamin D stores with a period of pharmacological high-dose calciferol therapy. Broadly speaking, one can divide the replenishment regimens into regular, low-dose treatment (e.g., 20,000 IU three times weekly for 8–12 weeks for adults) and intermittent, high-dose treatment (300,000 IU monthly for 3 months for adults). This intermittent high-dose therapy (known as "stoss" therapy in parts of continental Europe) can be an attractive option as poor patient concordance with therapy may be a problem, especially in asymptomatic individuals.

Several studies have investigated the difference between regular low-dose and intermittent high-dose therapy in relation to efficacy and safety profile (Table 2). Again, inconsistent results have been reported, perhaps because of the heterogeneous population groups studied and regimens selected. Whereas Hackman et al. [50] and Binkley et al. [40] reported similar serum 25(OH)D responses to both regular low-dose and intermittent high-dose regimens, Shakiba et al. [51] reported superior 25(OH)D levels with high-dose therapy compared to low-dose therapy, with the caveat that the study population was breast-fed infants. In contrast, Pekkarinen et al. [52] concluded that regular low-dose therapy was superior to intermittent high-dose therapy in improving 25(OH)D concentrations. Ilahi et al. [53] characterized the pharmacokinetics of a single, large dose of cholecalciferol (100,000 IU orally) and established that serum 25(OH)D concentrations peaked at 7 days, followed by a linear decline, returning to baseline by 84 days. The superior effects of regular-dose therapy may reflect a natural regulatory mechanism, with induction of 24-hydroxylase-mediated disposal and/or excess unbound plasma vitamin D being excreted more rapidly following an intermittent high dose [52].

Undoubtedly, the two dosing regimens differ in their pharmacokinetic trajectories. However, this may not be of much clinical significance because of the long serum half-life of 25(OH)D ($\sim$3 weeks) and its longer-term biological effects. It is also important for practitioners to be aware that compliance in clinical trials is likely to be superior to that in real-world clinical practice. Therefore, high-dose (dosing interval $\leq$2 months) and more regular low-dose regimens seem to offer similar efficacy in curing rickets and osteomalacia. However, where vitamin D is used to reduce the risk of falls and fractures in the elderly, the evidence favors daily oral vitamin D (800 IU) supplementation [54] rather than a single bolus annual dose of vitamin D (500,000/300,000 IU) [55, 56]. Physicians, therefore, should tailor the regimen to suit patient circumstances and the local availability of preparations.

What Is the Best Route of Administration, Intramuscular or Oral?

Both oral and intramuscular (IM) preparations of vitamin D are available. Although the oral route may be more convenient and physiological, the IM route may be useful in certain situations, specifically for intermittent high-dose regimens. In particular, although patients with malabsorption due to pancreatic insufficiency or celiac sprue can usually be adequately supplemented with appropriate doses of oral calciferols, individuals with short bowel syndrome may require intermittent IM dosing to achieve acceptable vitamin D status. Similarly, concordance with oral

Table 2 Low dose vs. high dose

Reference	Objective	Study population	Study design	Conclusion
Hackman et al. [50]	10 days × 50,000 IU vs. 3 months × 3,000 IU 25(OH)D checked at 3 months	59 Adult inpatients	RCT	Mean increases in serum 25(OH)D similar; no patient developed hypercalcemia, vitamin D toxicity, or nephrolithiasis
Pekkarinen et al. [52]	Daily × 800 IU vs. 97,333 IU × 4-monthly 25(OH)D checked at 12 months	40 Women (69.3–78.8 years)	RCT	Mean increase in serum 25(OH)D superior in low-dose, daily regimen

RCT randomized controlled trial

medication in elderly individuals in care homes or in children may be variable, and an intermittent once- or twice-yearly IM administration has proved effective in long-term prevention of deficiency [57]. On the other hand, Smith et al. [56] did not demonstrate any reduced rates of falls or fractures after annual IM 300,000 IU of D_2 administration. Romagnoli et al. [42] demonstrated that when vitamin D is given IM serum 25(OH)D levels do not increase rapidly within the first week, in contrast to oral administration. There was then a gradual increase in serum 25(OH)D levels from the first week to 2 months. This suggests that when vitamin D is given by the IM route there is a delayed and blunted serum 25(OH)D response. Diamond et al. [57] demonstrated that a single annual IM injection of 600,000 IU of vitamin D_3 was both safe and effective at improving the serum 25(OH)D level, i.e., >50 nmol/L.

The two routes clearly have different pharmacokinetics. Whereas the oral route leads to an increase in serum 25(OH)D levels within 3 days, the IM route leads to a sequestration in the muscle and fat with gradual release into the vascular system.

With IM vitamin D preparations currently in short supply in many health-care settings, oral administration should be considered the primary route for vitamin D replacement in most circumstances.

Special Considerations in Treating Children

Neonates born to vitamin D-deficient mothers can present with hypocalcemia in the neonatal period. Older children typically present with vitamin D deficiency at times of rapid skeletal growth, such as in the toddler years and during puberty. Hence, hypocalcemia or rickets in infancy and muscle cramps and fatigue in adolescence are a familiar picture to many pediatricians. The key to preventing vitamin D deficiency in children is to ensure that all women are supplemented with vitamin D during pregnancy and that all children are supplemented from the first weeks of life. Many children should remain on vitamin D beyond the first years of life, particularly those in the more northern latitudes and those with risk factors such as dark skin or chronic health issues that are associated with more time spent indoors. The Department of Health in the United Kingdom, as part of the Healthy Start scheme, recommends supplementary vitamin drops containing 400 IU of calciferol daily for all infants and preschool children [58]. In contrast to adults, in whom concurrent administration of calcium with vitamin D is warranted only in specific groups, in children with symptomatic rickets or hypocalcemic seizures additional replacement with daily calcium salts should be the rule. This is to avoid hypocalcemia during rapid mineralization of the skeleton ("hungry bone" syndrome) stimulated by calciferol therapy. A list of available preparations for treating and supplementing children is outlined in Table 3.

Long-Term Supplementation of Adults

Unlike children, adults do not undergo rapid skeletal mobilization and growth. However, vitamin D is still crucial for ensuring optimal bone health and muscle function. Specific groups such as pregnant and lactating mothers, >70-year-old adults, and those who are obese and on

Table 3 Treating and supplementing children

	Age group	Dose
Treatment		
Cholecalciferol	0–18 years	2,000 IU daily × 6 weeks[a]
Cholecalciferol	0–18 years	2,000 IU daily × 6 weeks[a]
Cholecalciferol	0–18 years	60,000 IU weekly × 6 weeks 300,000 IU once only (stoss therapy)
Supplementation		
Cholecalciferol	<6 months	400 IU daily[a,b]
Cholecalciferol	≥6 months	400–800 IU daily[a,b]

[a] Endocrine Society recommendations [6]

[b] Institute of Medicine recommendations [12]

Table 4 Treating and supplementing adults

	Dose
Treatment	
Cholecalciferol	10,000 IU daily × 8–12 weeks
Cholecalciferol	60,000 IU weekly × 8–12 weeks
Cholecalciferol	600,000 IU once or 300,000 IU twice (stoss therapy)[a]
Supplementation	
Cholecalciferol	1,000–2,000 IU daily[a]
Cholecalciferol	10,000 IU weekly
Cholecalciferol	300,000 IU once or twice annually[a]

Special considerations: Pregnant and lactating mothers: 1,500–2,000 IU daily. >70-year-old adults: 1,500–2,000 IU daily. Calcium cosupplementation effective for osteoporosis prevention. Obese children and adults and those on antiepilepsy drugs, glucocorticoids, antifungals, and antiretroviral therapy should be given twice to thrice the standard vitamin D doses. To convert IU to micrograms of calciferol, divide by 40. One-off high-dose treatments are effective but should be followed by a maintenance therapy dose of calciferol. However, caution must be employed in the elderly when administering large-bolus doses [55, 56]

[a] Endocrine Society recommendations [6]

medications that increase vitamin D catabolism are particularly vulnerable to deficiency; and long-term supplementation should be encouraged.

Table 4 summarizes the available regimens to replenish and supplement adults.

The maximum safe bolus and regular daily doses of calciferol remain uncertain. Cipriani et al. [59] specifically investigated the safety profile of a single oral dose of 600,000 IU of vitamin D_2 in young healthy adults and found no adverse events. Similarly, a 28-week incremental dose regimen in adults with multiple sclerosis using daily doses as high as 40,000 IU was found to be well tolerated with no change in serum calcium, despite mean serum 25(OH)D of 413 nmol/L [60]. On the other hand, a recent double-blinded, placebo-controlled trial showed an increase in falls and fracture rates in the elderly (>70 years) who were given a single oral annual dose of 500,000 IU of D_3 [55]. A further double-blinded, placebo-controlled trial showed no reduction in nonvertebral fractures but an increased risk of hip fractures in the elderly (>75 years) when given a single IM annual dose of 300,000 IU of D_2 [56]. Hence, there are emerging concerns regarding the safety profile of large, single doses of vitamin D in the elderly. This issue has been discussed in detail by Sanders et al. [55] Table 5.

Simply advising increased sun exposure or a change in diet as long-term prevention once vitamin D deficiency has been treated is generally futile. In many cases the patient will become symptomatic again, a year or two later. Thus, most patients who have suffered from symptomatic vitamin D deficiency should continue to take lower-dose vitamin D supplements throughout adult life, such as cholecalciferol 1,000–2,000 IU daily for an adult or 400–800 IU daily for a child. Although intermittent high-dose IM therapies, such as ergocalciferol 300,000 IU once or twice yearly, are popular modes of ongoing supplementation in the elderly population, they should be used with caution in view of recent trials [55, 56]. Use of combined calcium and vitamin D preparations should generally be avoided in adults as dietary calcium intake is already adequate in most Westernized countries and the calcium component of combined preparations makes the tablets unpalatable for long-term use. However, certain groups, such as the elderly, those requiring osteoporosis prophylaxis, pregnant women, and those on a particularly calcium-poor diet (lactose intolerance), should receive additional calcium supplementation.

Table 5 List of currently available preparations in the United Kingdom

Solution/drops
Dalivit cholecalciferol 400 IU/ 0.6 mL[a]
Abidec cholecalciferol 400 IU/ 0.6 mL[a]
Healthy Start vitamin drops cholecalciferol 300 IU/ 5 drops[a]
Ergocalciferol oily solution 3,000 IU/ mL
Tablets/capsules
Calcium and vitamin D (400 mg calcium + 400 IU ergocalciferol)
Cholecalciferol 800 IU (Fultium D_3)
Cholecalciferol 20,000 IU (Dekristol, MIBE)
Ergocalciferol 10,000 or 50,000 IU (UCB pharma)[b]
Parenteral
Ergocalciferol 300,000 IU/mL

[a] Multivitamin preparations; not suitable for prolonged high-dose therapy as may lead to vitamin A toxicity

[b] Market availability intermittent

Conclusions

Vitamin D insufficiency and deficiency remain frequent problems affecting, to differing degrees, a large proportion of the populations of many countries, both affluent and developing. This indicates a widespread failure of public health policy in many societies. Population vitamin D status could be improved by more generalized food supplementation or clearer advice about the benefits of appropriate sunlight exposure. Public health policies need to be tailored to local dietary customs, prevalent UVB exposure, and dress habit. In particular, oral vitamin D intakes recommended for the U.S. or Australian population are not appropriate for northern European populations, who are exposed to substantially lower-intensity sunlight. However, there is conflicting information regarding sunlight, vitamin D preparation, dose, and dosing interval when attempting to attain and maintain optimal serum 25(OH)D levels. This reflects, at least in part, differences in study design, preparation selected, dosing interval, and the population and age group studied.

One can conclude that sunlight in isolation is insufficient to generate adequate vitamin D production in most people living in northern latitudes, including the United Kingdom. Diet is a poor source of vitamin D for most of the population. We believe that the current evidence suggests that cholecalciferol has modest advantages over ergocalciferol as a means of increasing serum 25(OH)D levels. Regular, low-dose and intermittent, high-dose vitamin D preparations are equally effective, provided the dosing interval with the latter is less than 2 months. Concerns have also been raised recently regarding the safety profile of single large-dosage calciferol regimens in the elderly. The oral route is superior to the IM route in the administration of calciferol because of its convenience, rapid absorption, and effect of increasing serum 25(OH)D levels. Finally and most importantly, the choice of therapy should be tailored

to the patient's circumstances, degree of vitamin D deficiency, and the vitamin D preparations available locally.

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