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POSITION PAPER

Optimisation of vitamin D status in global populations

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Abstract
Vitamin D is important for musculoskeletal health. Concentrations of 25-hydroxyvitamin D, the most commonly measured metabolite, vary markedly around the world and are influenced by many factors including sun exposure, skin pigmentation, covering, season and supplement use. Whilst overt vitamin D deficiency with biochemical consequences presents an increased risk of severe sequelae such as rickets, osteomalacia or cardiomyopathy and usually warrants prompt replacement treatment, the role of vitamin D supplementation in the population presents a different set of considerations. Here the issue is to keep, on average, the population at a level whereby the risk of adverse health outcomes in the population is minimised. This position paper, which complements recently published work from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases, addresses key considerations regarding vitamin D assessment and intervention from the population perspective.

Summary This position paper, on behalf of the International Osteoporosis Foundation Vitamin D Working Group, summarises the burden and possible amelioration of vitamin D deficiency in global populations. It addresses key issues including screening, supplementation and food fortification.

Keywords Cholecalciferol · Deficiency · Ergocalciferol · Population · Supplementation · Vitamin D

Introduction

Much has been written about the role of vitamin D in musculoskeletal health, predominantly in the context of interventions for patients, that is, with a paradigm of disease rather than of population health. However, given the substantial variation in 25-hydroxyvitamin D concentrations globally both across and within populations, and that sunshine exposure, food fortification and supplements provide readily available interventions to raise vitamin D concentrations, it is apparent that the problem should be addressed not just for individual patients who might have symptomatic disease, but at the population level. This narrative review article constitutes a Position Paper on behalf of the Vitamin D Working Group of the International Osteoporosis Foundation Committee of Scientific Advisors, and complements a comprehensive review of vitamin D in musculoskeletal disease, recently published by a Working Group from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases [1]. The present review addresses the latest findings on variation in global 25-hydroxyvitamin D concentrations, key issues around measurement assays and standardisation, considerations relating to supplementation and food fortification, and merits of screening versus population intervention.

Global variation in vitamin D concentrations

Vitamin D deficiency and associated public health and clinical consequences are recognised as a global issue. Despite this, the uniform achievement of adequate vitamin D status through diet and safe sunshine exposure remains a challenge to clinicians and public health experts. Across world regions and ethnic groups, there remains a paucity of consistently ascertained representative population data addressing measurement of 25-hydroxyvitamin D [25(OH)D], the principal circulating storage form of the hormone [2, 3]. For an introduction to vitamin D biology the reader is referred to [4].

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Whilst there are differences in definitions of deficiency, it is generally accepted that serum levels of 25(OH)D below 25nmol/L are indicative of increased risk for musculoskeletal disease, for example, rickets and osteomalacia. Another important factor, often overlooked, is the contribution of dietary calcium intake to the development of such vitamin D-associated outcomes [5–7]. Furthermore, measurement of parathyroid hormone, which if raised, may indicate a biochemical consequence of vitamin D deficiency, is often lacking from surveys [4]. For the purposes of this review, deficiency is defined as a 25(OH)D level below 25nmol/L (as per Scientific Advisory Committee for Nutrition (UK), European Food Standards Agency (EFSA), Institute of Medicine (USA)) [8–10]. Some, but not all, regulatory bodies propose 50 nmol/L as a population preventative level, and so in the description of prevalence below, studies using this cutoff will also be considered [11].

Recent reviews on global prevalence provide an excellent framework from which to understand the clear gaps in documentation of vitamin D deficiency worldwide [3, 11–13]. A major methodological issue is the assessment method used to determine vitamin D status. The Vitamin D Standardisation Program (see below) has worked to harmonise approaches and produce clear guidance for the assessment of 25(OH)D levels [14]. In a recent survey of global levels, it was apparent that Latin America, Oceania and North America have relatively low prevalence of serum 25(OH)D below 25 nmol/L, ranging from 5-18% [3]. In contrast, the prevalence of these low levels in Europe, Asia and Africa ranged from 24% to 49% [3]. Data from Finland and the UK all clearly show the greater prevalence of vitamin D deficiency in ethnic groups with darker skin. In Finland for example, prevalence of 25(OH)D <30 nmol/L was 4.5% in Russian speaking migrants, compared to 28.0% and 50.4% in Kurdish and Somalian migrants respectively [3]. A recent review of 25(OH)D levels in low- and middle-income countries found marked heterogeneity in levels, and 54 of 83 countries had no 25(OH)D data suitable for study [12]. Indeed prevalence of levels below 30 nmol/L amongst Indian preschool children was 14%, rising to 24% of adolescents [15]. Meta-analysis of levels in Africa also demonstrated heterogeneity [16]. It should be noted that Africa has an ethnically and geographically diverse population with over 3000 ethnic groups in more than 50 countries. Indeed, many population groups were missing from the available data, for example adolescents and older adults, and most data were from North African countries and South Africa, meaning sub-Saharan Africa was under-represented.

It is tempting to interpret global prevalence estimates simply in relation to sunlight exposure, skin pigmentation and covering. However, it is apparent from these estimates that there is not simply a latitude-dependent relationship, but dietary elements, particularly related to calcium and vitamin D nutrition, are also important [3]. For example Finland and Canada have mandatory food fortification with vitamin D, and some northern coastal populations may habitually have greater vitamin D content in the diet; in contrast, in many African countries, habitual dietary calcium intake is extremely low, which increases the risk of skeletal sequelae even in the context of 25(OH)D concentrations which would otherwise be viewed as adequate [3].

Methodological issues with 25(OH)D testing: assay variability, standardisation and a call to action

It is widely accepted that the circulating 25(OH)D concentration is the best measure of an individual's vitamin D status [17]. However, it has long been recognised that the 25(OH)D value obtained on a single sample may vary substantially, dependent upon the assay used and laboratory in which it is measured. This recognition led, in 1989, to the development of the Vitamin D External Quality Assessment Scheme (DEQAS), whose objective is to ensure analytical reliability of 25(OH)D and $1,25(OH)_2D$ assays [18]. Subsequently, the Vitamin D Standardisation Program (VDSP) was begun in 2010 to coordinate an international effort to standardise 25(OH)D measurement to gold standard reference measurement procedures (RMPs) [19]. In 2013, DEQAS focused on accuracy, with 25(OH)D values assigned for all samples by the US National Institute of Standards and Technology (NIST) RMP; i.e. the true concentration. Unfortunately, despite these efforts, substantial between and within assay variability persists. This variability has contributed to the difficulty in defining deficiency, hampered surveys of comparative levels, for example by geographic location, ethnicity and over time, and confounds attempts at meta-analyses using published 25(OH)D results. This variability has also contributed to marked variation in recommendations from the over 40 vitamin D guidelines worldwide [20, 21]. Indeed, a moratorium on meta-analyses of 25(OH)D levels has been proposed [22], with a call for reporting standardised measures in new studies [11, 23, 24], in order to address key challenges facing those who attempt to develop clinical or public health recommendations [25]. One journal already requires reporting standardised 25(OH)D measures as a condition of publication [26]. Without the adoption of such an approach journal-wide, the scientific value of the many emerging articles addressing vitamin D will continue to be substantially under-realised. In support of this call to action [11, 23, 24], it is therefore recommended that all journals require the reporting of standardised 25(OH)D values, according to VDSP guidance, in any articles in which this analyte is measured.

Vitamin D supplementation

Pharmacokinetics and pharmacodynamics

The two most common forms of oral vitamin D are plant-derived ergocalciferol (D_2) and animal-derived cholecalciferol (D_3). Whilst vitamin D_2 and D_3 are often considered to be equivalent, there are differences. The affinity of the vitamin D binding protein (VDBP) for vitamin D_2 metabolites is slightly less than for vitamin D_3 which likely leads to approximately 10% shorter half-life of 25(OH)D_2 compared with 25(OH)D_3 [27]. Moreover, a systematic review of studies comparing vitamin D_2 and vitamin D_3 supplementation found cholecalciferol to produce greater increments in circulating total 25(OH)D concentration than does ergocalciferol [28]. In addition, 25(OH)D_2 may not be accurately measured with kit-based assays or automated analysers that are often used in clinical laboratories. Therefore, in the absence of other specific considerations, in general cholecalciferol is the preferred form for clinical use [29]. In pharmacokinetic studies the serum half-life ($T_{1/2}$) of cholecalciferol is 20 h, 25(OH)D_3 (calcifediol) is 15 days and 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] (calcitriol) is 4 to 6 h [27]. In addition, oral intake of calcifediol increases circulating 25(OH)D faster than cholecalciferol by a factor of 3.2 [27, 30] possibly as a consequence of being relatively less lipophilic.

Mechanisms of potential toxicity with vitamin D dosing

Bolus or loading doses of vitamin D_3 are used to rapidly replete vitamin D deficient adults, and they are sometimes prescribed based on patient preference. Such approaches are clearly most relevant in the context of patients presenting with clinical symptoms rather than addressing vitamin D status at the population level. Indeed, the physiological effects of bolus dosing and its impact on musculoskeletal health suggest that bolus dosing is unlikely to be the optimal approach either for patients or for population supplementation. Thus, bolus dosing must be undertaken with care to avoid adverse musculoskeletal consequences [31]. Bolus doses of vitamin D can increase circulating levels of FGF23 [32], an osteokine produced mainly in the osteocyte that regulates phosphorus and vitamin D metabolism in the kidney. FGF23 downregulates 1α-hydroxylase (CYP27B1) and upregulates 24-hydroxylase (CYP24A1), with the net effect of inadequate 1,25$(OH)_2$D despite adequate or high levels of 25(OH)D [33]. Degradation of 1,25$(OH)_2$D results in decreased calcium absorption, increased bone turnover, bone loss and fractures. In recent trials of bolus doses of vitamin D, the intervention has actually appeared to increase the risk of falls [34, 35] and fractures [34]. Although FGF23 was not measured in these studies, FGF23 may have had a role in their untoward outcomes. Higher FGF23 levels have also been associated with increased risk of frailty [36].

A recent study illustrates the impact of bolus vs daily vitamin D dosing on circulating 25(OH)D levels [37]. In this study, the same cumulative dose of vitamin D_3 was given as either 2000 IU/d or 50,000 IU/mo for 75 days to 60 healthy young adults. The 25(OH)D levels in the two groups were similar at baseline (~35 nmol/L), on day 25 (~70 nmol/L), and thereafter; however, the levels differed over the first 2 weeks of treatment. The monthly dose caused a rapid ~22.5 nmol/L increase in 25(OH)D after only 2 days, whereas the daily dose had increased 25(OH)D by only 5 nmol/L at day 2. The 1,25$(OH)_2$D levels also rose rapidly, within 2 days, in the monthly dose group; serum FGF23 levels did not increase in either group [37]. In an earlier study, amongst 48 women (mean age 81 years) randomised to oral cholecalciferol at 1500 IU daily, 10,500 IU once weekly, or 45,000 IU once every 28 days, achieved increases in 25(OH)D at 2 months were similar among the groups [38]. Whilst these studies demonstrate that these different regimens can be similarly effective, with possible support for more rapid onset from bolus dosing, they clearly have far too few participants to inform any safety outcomes.

Overall then, in the context of a population approach, daily dosing with cholecalciferol or ergocalciferol at modest doses of around 800–1000 IU/day is likely to be effective at preventing frank vitamin D deficiency, and extremely unlikely to cause adverse effects. This intake range is consistent with current IOF recommendations [39] and recommendations of the then US Institute of Medicine (IOM; now National Academy of Medicine, NAM) [9]. For fracture risk reduction; however, vitamin D alone does not appear to be effective [40, 41]. In contrast, combined supplementation with vitamin D and calcium, in doses of 400–800 IU and 1000–1200 mg per day, respectively, lowered hip fracture risk by 16% and fracture risk by 6% in older adults with insufficient intakes [40]. In many regions, substantial proportions of the population are low in intake of both vitamin D and calcium [2, 3, 42]. In these regions, it may therefore be reasonable to increase intake of both nutrients.

Bolus doses are not generally recommended unless there is a specific need for rapid correction in the context of an appropriate evaluation of the benefits and risks of this approach. A further consideration with regard to supplementation is the regulatory basis of the supplement itself. In many countries, food supplements are subject to substantially more relaxed regulation, in terms of specified content, compared with medicines. Indeed, there may be a marked divergence of actual compared with advertised vitamin D content in a range of over-the-counter supplements [43]. It is therefore reasonable that where vitamin D supplementation is recommended by a medical professional, a licensed product (subject to rigorous manufacturing regulation) is used.

Food fortification

Cholecalciferol and ergocalciferol are both naturally occurring micronutrients found in normal diets. As such, one approach which has been espoused for the optimisation of population vitamin D status is that of food fortification. This is particularly so because of the increased risk of skin cancer with excessive sun exposure if used as a route to vitamin D formation. Such an approach has been introduced in the USA, Canada, Finland, India and several countries in the Middle East-North African region, amongst others, mandating the addition of vitamin D to cow's milk, margarine and other dairy products, together with orange juice and cereals [44]. In Finland the effect of fortification has been objectively assessed through a prospective survey of population levels, linked with the Vitamin D Standardisation Program [45]. Thus, mean serum 25(OH)D concentrations increased from 47.6 to 65.4 nmol/L over the decade from 2000 to 2011, although there was a concomitant increase in supplement use from 11 to 41% over this time. A recent systematic review of data from 34 publications suggests a benefit to food fortification approaches with a pooled 25(OH)D increase of 21.2 nmol/L (95% CI: 16.2, 26.2) [46]. Furthermore, in a study pulling together data from 20 randomised controlled trials and 20 national health surveys as well as prospective cohort studies, for the EU-funded ODIN project, adverse events, including excess 25(OH)D, were extremely rare with food fortification, and less than with formal supplementation approaches [47]. Although the cost effectiveness of such approaches is uncertain, and will of course vary markedly between countries, a further benefit to food manufacturers, in a climate in which greater vitamin D intake is viewed favourably by consumers, is the likely attraction of new products incorporating vitamin D fortification [44, 48]. In summary, although specific implementation strategies may need to be developed for individual countries, food fortification approaches, in the context of appropriate monitoring, may offer a relatively safe and efficient means to increasing population levels of 25(OH)D.

Population health approaches

Current guidelines

There are several key sets of guidelines internationally providing recommendations around adequate plasma 25(OH)D concentrations. In comparing these guidelines, it is extremely important to appreciate whether the target is the population as a whole, or individuals with specific diseases [1], for example osteomalacia or osteoporosis. At a population level, recommendations are developed as preventative measures, and are derived overall to prevent a specific disease or set of diseases. In the majority of current vitamin D guidelines, the aim is to prevent musculoskeletal outcomes such as rickets, osteomalacia, osteoporosis, fractures and/or falls. Very few data exist currently to base the guidance on prevention of any other disease in the population [49]. When considering how to achieve population sufficiency in 25(OH)D status, sources of vitamin D should be considered. The primary determinant of 25(OH)D status is through dermal synthesis, and in many populations achieving adequate status using natural food sources alone is extremely difficult. There is insufficient evidence for recommendations to include safe levels of sunlight exposure, and so guidelines generally consider adequate dietary intakes only [8], through natural food sources or fortification.

Before considering specific vitamin D intake recommendations it is important to note how a dietary recommendation is presented. For example, as set out by the World Health Organization, the "Estimated Average Requirement" (EAR) denotes the average daily intake that meets the needs of 50% of "healthy" individuals in a particular age and gender group. The "Reference Nutrient Intake" (RNI) is the intake that will be adequate to meet the needs of 97.5% of the population [50], an equivalent concept to that of the "Recommended Daily Allowance" (RDA) or "Reference Daily Intake" (RDI) used by the Food and Nutrition Board of the United States National Academy of Sciences [50, 51].

Intake recommendations have been developed for the general population and for individuals with or at increased risk for musculoskeletal disorders. The US National Academy of Medicine provided vitamin D intake recommendations for the general population as follows: for ages 51 to 70 years, 15 µg (600 IU) per day, and for age 71 years and older, 20 µg (800 IU) per day [52]. This was accompanied by a recommendation of a target 25(OH)D level of 50 nmol/L to meet the needs of 97.5% of the population. The UK Scientific Advisory Committee on Nutrition focused population prevention of the most severe deficiency (<25 nmol/L) within the population, recommending a RDI for individuals 4 years old or above of 400 IU (10 µg) daily [8]. Other organisations have made recommendations for people at risk for musculoskeletal disorders, for example osteoporosis. These organisations, including the Endocrine Society [53], the International Osteoporosis Foundation [39] and the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis ESCEO [54], recommend a target level of 75 nmol/L. The International Osteoporosis Foundation recommends vitamin D supplementation for seniors aged 60 years or older, who are generally at increased risk of musculoskeletal disorders, at a dose of vitamin D_3 of 800 to 1000 IU/day to benefit bone health and help reduce the risk of falls [39]. For those with osteoporosis for example, supplementation would be alongside definitive treatment for the condition, such as with an antiresorptive medication.

In summary, the prevailing view from national and societal guidelines more often recommends achieving adequate status through dietary intake, and if this cannot be achieved, to recommend supplementation with modest doses of vitamin D. In any guideline, clearly it is important that the population group to which the guidelines are targeted, and the outcomes addressed, are clearly communicated.

Population screening/supplementation

The original ten principles underlying implementation of a screening programme, conceptualised by Wilson and Jungner [55], are summarised in Table 1. There is clearly much debate about these points in the context of vitamin D deficiency. It is well established that there is an increased risk of musculoskeletal adverse outcomes such as osteomalacia and proximal myopathy in severe deficiency. However, despite many documented associations based on observational data, there is very little support for a causal relationship between vitamin D deficiency and many other outcomes across most organ systems [57]. The justification for screening in terms of health outcomes therefore is clearly dependent on the degree to which one believes in a causal link between vitamin D deficiency and the particular health outcome(s) in question. Indeed randomised controlled trials such as RECORD [58], VITAL [59, 60], DO-HEALTH [61], ViDA [62] and D2D [63], with large doses of vitamin D supplementation, have demonstrated no benefits across a wide range of health outcomes including cancer, cardiovascular and musculoskeletal diseases, albeit in the context of healthy, generally vitamin D replete populations, rather than those with frank vitamin D deficiency. The efficacy of such interventions in a vitamin D-deficient population therefore remains uncertain.

What is much less controversial is that vitamin D deficiency is easily prevented and treated, either with supplements, or at the population level, arguably more appropriately with food fortification or lifestyle changes. Vitamin D deficiency may be evaluated in laboratory to establish whether an individual is below a certain 25(OH)D concentration (noting the analytical issues as mentioned above), although ascertaining whether this is definitely having a functional effect (concomitant measurement of calcium concentrations, inorganic phosphate concentrations and parathyroid hormone may assist here) is not always straightforward [29]. Thus, there is a suitable test and the test is likely to be acceptable to the population, with this able to characterise the latent stage of the "disease". However, the relationship between a 25(OH)D measurement and disease is still very uncertain at the individual level, with many of those who have 25(OH)D concentrations less than 25 nmol/L likely to be healthy, particularly where calcium intake is adequate [49, 64]. Furthermore, it is apparent from the heterogeneity in guidelines and definitional approaches globally that there is little agreed policy on whom to treat, and indeed how to treat. National differences in cost of treatment, healthcare systems and reimbursement have a major impact on the health economic viability of interventions. A very important consideration in terms of screening is thus the balance between the cost of treatment versus the cost of the measurement. Given that a 25(OH)D assay may cost an order of magnitude more than several months' supply of vitamin D supplement, in the context of evident safety for modest supplemental doses, and uncertain benefit, the justification for widespread testing is weak. Furthermore, vitamin D supplementation may be procured by individuals themselves rather than through the health service, in response to government guidance.

Overall, screening via measurement of 25(OH)D in the general population seems poorly justified. Indeed, increasing vitamin D testing has placed an increasing monetary burden on healthcare systems, with recent reviews suggesting that substantial proportions are clinically inappropriate [65–68]. For example an Australian study estimated that there were almost 3.5 million unnecessary vitamin D tests in 2020 amounting to a cost of more than AUD87 million (~USD56

Table 1 The original ten principles for a screening programme outlined by Wilson and Jungner [55, 56]

1	The condition sought should be an important health problem.
2	There should be an accepted treatment for patients with recognised disease.
3	Facilities for diagnosis and treatment should be available.
4	There should be a recognizable latent or early symptomatic stage
5	There should be a suitable test or examination.
6	The test should be acceptable to the population
7	The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8	There should be an agreed policy on whom to treat as patients.
9	The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole
10	Case-finding should be a continuing process and not a "once and for all" project.

million) and generating a carbon footprint equivalent to driving up to 230,000 km in a standard passenger car [65]. In Manitoba, testing appeared to quadruple between 2006 and 2013 with unnecessary testing increasing by over 30% [66]. All these considerations fuel the important question of whether vitamin D testing should be carried out, and when supplementation may be initiated in its absence.

However, there is potentially more rationale for undertaking this approach in populations who are most at risk of severe vitamin D deficiency and its sequelae, such as osteomalacia and muscle weakness in adults, and hypocalcaemia, cardiomyopathy, myopathy, osteomalacia and rickets in children. For example, in the northern hemisphere, populations with pigmented skins, who habitually cover the majority of skin with clothing, could be considered for such a policy. Here again though it could be argued that, in the absence of a clinical presentation, habitual supplementation with vitamin D, perhaps at higher level than in a White population, might offer a more economically efficient strategy. For example, the Endocrine Society recommends screening people at risk, including African Americans and Hispanic, pregnant and lactating women, older adults with a history of falls or non-traumatic fractures and patients with a number of diseases involving the skeleton [53].

The US Preventive Services Task Force (USPSTF) systematically reviewed benefits and harms of vitamin D screening in asymptomatic adults [69, 70]. They found no direct evidence of effects of screening versus no screening on clinical outcomes, but that treatment in asymptomatic persons might reduce the risk of death and falls in institutionalised elderly persons [69, 70]. However the USPSTF has recommended against routine vitamin D supplementation to prevent falls in community-dwelling adults aged ≥65 years based on inconsistent findings from five clinical trials, which included one trial reporting increased risks of both falls and fractures among people who supplemented with vitamin D [69, 70]. Fundamentally, health economic studies of vitamin D supplementation are heavily influenced by prior belief in causal associations between vitamin D deficiency and a range of outcomes, which, as described above, are not well supported beyond the musculoskeletal system. Other factors such as differences in dose, mode of administration, cost of supplementation, healthcare settings and willingness to pay all influence outcomes [69–72].

When deciding whether or not to recommend ubiquitous supplementation or fortification strategies for prevention of vitamin D deficiency in the general population it is important to consider population and context specific requirements, noting that one size does not fit all. As has been discussed already in this review, there are many guidelines across the globe, each with differences in what it is trying to achieve and which groups it identifies as at risk. An example can be drawn from populations with habitually low calcium intakes, where calcium supplementation to achieve international standards has resulted in unanticipated findings. For example, in a pregnancy trial in The Gambia, where background dietary calcium intakes are habitually extremely low, mothers who were allocated calcium supplementation during pregnancy lost more bone during lactation than did those who took placebo, and female offspring grew slower, whereas boys grew faster [73]. In the same population, supplementation during childhood did not have lasting effects on bone, but boys who took calcium went into puberty earlier, and, as a consequence were shorter at the end of growth than those who took placebo [74]. These data caution against a single approach to supplementation.

Conclusion

Emerging studies, some of which used standardised approaches to vitamin D measurements, have suggested substantial heterogeneity in average 25(OH)D levels around the world and that these are dependent on a range of factors such as diet and covering, as well as latitude and effective sun exposure. Vitamin D epidemiology, and indeed synthesis of guidelines, would be substantially strengthened by the adoption of a requirement to report standardised 25(OH)D levels in journal articles. Although low levels of 25(OH)D are relatively common, overt musculoskeletal sequelae are rare in many populations. Overall, active screening for vitamin D deficiency at the population level, in the absence of a clinical presentation, does not appear to be justified. Approaches to increasing vitamin D levels in the population may focus on food fortification, and/or supplemental approaches, either through managed programmes or encouragement for self-administration. More active approaches may be warranted in populations at very high risk of severe deficiency, for example individuals with pigmented skin living at higher and lower latitudes from the equator. Importantly any intervention should account for population characteristics, for example habitual calcium intake. Clearly, at the individual patient level, where there is a clinical presentation suggestive of vitamin D deficiency, testing is likely to be indicated, together with a more aggressive approach to repletion.

Key points

- Vitamin D status, as assessed by 25(OH)D concentration, varies widely across the world, with key influences from latitude, season, sunlight exposure, skin pigmentation and covering, as well as dietary intake.
- Calcium intake, which varies widely globally, interacts with 25(OH)D concentration in determining adverse consequences of vitamin D deficiency.

- Comparisons of 25(OH)D levels between populations and over time have been hampered by analytical variation between assays.
- Standardised measures of 25(OH)D (as per the Vitamin D Standardisation Programme) should be reported in all publications documenting this biochemical analyte.
- Where supplementation is used in the context of healthy community dwelling individuals, daily oral doses of around 800–1000 IU cholecalciferol are recommended.
- Where supplementation is recommended by a medical professional it should be in the form of a licensed product to ensure consistency between prescribed and actual dose.
- Owing to evidence of associated increased risk of falls and fractures, in general, high-dose bolus approaches to vitamin D repletion are not recommended.
- Maintenance of adequate vitamin D status at the population level is obtained preferably through diet and lifestyle measures.
- Food fortification may provide alternative routes to optimising vitamin D status at the population level.
- On the current evidence base, there is insufficient justification for screening for vitamin D deficiency, or routine vitamin D supplementation, in the general population to prevent outcomes other than vitamin D deficiency.
- Screening and/or routine supplementation may be appropriate in high-risk populations, for example older individuals in residential care and those with pigmented skin living in northerly latitudes.

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