REVIEW

Vitamin D and musculoskeletal health: outstanding aspects to be considered in the light of current evidence

Marcela Moraes Mendes[1,2,3], **Patricia Borges Botelho**[1] and **Helena Ribeiro**[4]

[1]Department of Nutrition, Faculty of Health Sciences, University of Brasília, Distrito Federal, Brazil
[2]Department of Nutrition, Institute of Life Sciences, Federal University of Juiz de Fora, Governador Valadares, Minas Gerais, Brazil
[3]Department of Nutrition, Faculty of Health and Medical Sciences, University of Surrey, University of Surrey, Guildford, UK
[4]Department of Environmental Health, Faculty of Public Health, University of São Paulo, São Paulo, Brazil

Correspondence should be addressed to M M Mendes: m.moraesmendes@surrey.ac.uk

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Abstract

Vitamin D enhances calcium absorption and bone mineralisation, promotes maintenance of muscle function, and is crucial for musculoskeletal health. Low vitamin D status triggers secondary hyperparathyroidism, increases bone loss, and leads to muscle weakness. The primary physiologic function of vitamin D and its metabolites is maintaining calcium homeostasis for metabolic functioning, signal transduction, and neuromuscular activity. A considerable amount of human evidence supports the well-recognised contribution of adequate serum 25-hydroxyvitamin D concentrations for bone homeostasis maintenance and prevention and treatment strategies for osteoporosis when combined with adequate calcium intake. This paper aimed to review the literature published, mainly in the last 20 years, on the effect of vitamin D and its supplementation for musculoskeletal health in order to identify the aspects that remain unclear or controversial and therefore require further investigation and debate. There is a clear need for consistent data to establish realistic and meaningful recommendations of vitamin D status that consider different population groups and locations. Moreover, there is still a lack of consensus on thresholds for vitamin D deficiency and optimal status as well as toxicity, optimal intake of vitamin D, vitamin D supplement alone as a strategy to prevent fractures and falls, recommended sun exposure at different latitudes and for different skin pigmentations, and the extra skeletal effects of vitamin D.

Key Words

- 25(OH)D
- bone health
- vitamin D
- skeletal health

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Introduction

Vitamin D is vital to bone health, and prolonged severe deficiency can lead to rickets in children and osteomalacia/osteoporosis in adults (1, 2, 3). Vitamin D is an exceptional nutrient in that its primary source is the exposure of the skin to UV rays, whilst it can also be ingested through diet (1, 2, 3).

Over the past two decades, there has been intensifying robust scientific evidence that vitamin D inadequacy is a significant public health issue not only across all ages and ethnic groups but also across different latitudes around the world (4, 5, 6, 7, 8, 9). While this has led to an increasing interest in vitamin D amongst the scientific

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community, governmental advisory bodies, the food and supplement industries, and more notably the general public, recommendations for vitamin D adequate status as well as dietary intake and sunlight exposure remain mainly controversial and are still much debated (7, 10).

The current challenge in reaching a consensus on recommendations for vitamin D is primarily due to the lack of a robust comprehension of the actual contribution of sunlight exposure and dietary intake, from both food and supplements, on vitamin D concentrations according to the local environment and individual behaviour or lifestyle, and the differences in factors influencing vitamin D status, particularly between different groups (11, 12, 13). In addition, the variability in assessment methods and the influence of baseline levels thwart direct comparisons between studies conducted in different locations and population groups (14, 15).

The aim of this paper was to review the literature published, in the last 20 years, on the effect of vitamin D and its supplementation for musculoskeletal health, in order to identify the aspects that remain unclear or controversial and therefore require further investigation and debate. A literature search was performed in the Medline database (via PubMed) with the following keywords: vitamin D, 25-hydroxyvitamin D, musculoskeletal health, skeletal health, and bone health. We have selected studies investigating the effects of vitamin D on bone health, musculoskeletal markers, osteoporosis, fractures, and falls in otherwise healthy individuals.

Vitamin D endogenous production

Vitamin D is the generic term for two different molecules, ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3). Ergocalciferol is derived from UVB radiation on ergosterol, largely distributed in plants and fungi. In contrast, cholecalciferol is formed from the action of UVB rays in the skin and is therefore present in animal origin foods as well (3).

The cutaneous vitamin D synthesis mainly depends on UVB radiation reaching a 7-dehydrocholesterol molecule in the epidermis (16, 17, 18, 19). The UVB radiation level is a function of the sun's position in the sky – the higher the sun in the sky, the higher the UV radiation level – varying with the time of day and time of the year (season). The Earth's tilted position with respect to its orbit around the sun, along with its yearly revolution and inherent daily rotation, determines the distribution of solar radiation over its surface. The solar zenith angle decreases with proximity to the equator, reducing the path length of sunlight through the atmosphere and consequently increasing the effective level of UV radiation (16, 17, 18, 19). There is no UVB radiation in high latitude countries from the end of October to March. In contrast, this wavelength has abundant radiation in low latitude countries throughout all year (16, 17, 18, 19).

In summer, due to the sun's higher position in the sky, its rays hit the Earth more directly; therefore, less radiation is spread out. In contrast, the sun appears low in the sky during winter, spreading its rays out over a much wider area, becoming less effective (16, 20). Accordingly, seasonal cycling of serum 25-hydroxyvitamin D (25(OH)D) concentrations has been shown in countries at mid-high (20, 21) as well as in low tropical latitudes (22, 23).

A two-centre cohort study with 518 postmenopausal women (age 55–70 years) assessed serum 25(OH)D at fixed three-monthly intervals from summer 2006 and observed significant local, seasonal, and ethnic differences in vitamin D status in postmenopausal women at high latitudes (18). In lower latitudes, the same seasonal variation is observed, and although the minimal sunlight radiation during wintertime is still of high enough levels for adequate vitamin D production, the seasonal cycle in 25(OH)D concentrations has also been reported in such locations (22, 23, 24).

Considering this seasonal variation, dietary intake and vitamin D supplementation for the general population might be required throughout winter to maintain adequate serum concentrations in higher latitudes (11, 13). In most countries, the major dietary sources of vitamin D include oily fish, meat, fortified breakfast cereals, and fat spreads (e.g. margarine). Therefore, individuals who avoid consuming animal source foods, such as vegetarians and vegans, could have lower 25(OH)D concentrations in comparison with meat and fish eaters, if not receiving any type of vitamin D supplementation, as seen in several small studies conducted among Europeans (25).

Although adequate vitamin D intake and supplementation during the winter is the recommendation to tackle the low level of UVB during the winter and avoid deficiency, current research has also proposed the hypothesis that the passaging of 25(OH)D in and out of muscle cells is influenced by vitamin D-binding protein (DBP). This process might lead to considerable persistence of 25(OH)D in the circulation, with recent evidence showing that this is enhanced in winter. This mechanism would in turn support adequate vitamin D status during the seasonal interruption of vitamin D endogenous production from sunlight exposure. Moreover, it has been

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proposed that this sort of storage could be compromised if muscle function deteriorates due to a lack of exercise or malnutrition (26, 27).

Even though endogenous synthesis through exposure to sunlight radiation is essential to maintain vitamin D levels, detrimental effects on our cells also occur concomitant to vitamin D production. The earliest humans evolved in environments with extremely high UV radiation from the sun in equatorial Africa and were dark-skinned. Living at the equator, these primitive populations, therefore, received high amounts of UV radiation. However, the melanin in their skin – responsible for skin pigmentation – functioned as an effective natural sunscreen against the cell degradations of sunlight exposure, still allowing for vitamin D production (3, 12, 16).

As humans dispersed over time across the globe, they faced very different sunlight radiation in the new high-latitude territories, in both intensity and seasonality, and significantly colder climate. During wintertime, the sun's rays reach the Earth at a more oblique angle in high latitude locations, taking a longer path through the atmosphere and are consequently less intense. Indeed, nearly no UVB (the adequate wavelength to produce vitamin D in the skin) is available at this time of the year at latitudes above 40°. It is thus hypothesised that lightly pigmented skin evolved through time to adapt to the effects of the high latitude environment and optimise vitamin D production to maintain bone health (12, 16). Therefore, there is an urgent need to better comprehend the influence of individual factors on vitamin D production via sunlight exposure. Besides local availability, several other factors may determine this production.

Factors affecting individual UV radiation levels and consequently the endogenous synthesis of vitamin D

Skin pigmentation can greatly reduce the UV-mediated synthesis of vitamin D. Cutaneous melanin pigment in human skin naturally competes for and absorbs the UVB photons responsible for the photolysis of 7-dihydrocholesterol to pre-vitamin D_3. Therefore, individuals with higher melanin (i.e. dark-skinned) content in their skin require more UV light exposure to synthesise the same amount of vitamin D_3 as individuals with less melanin (i.e. fair-skinned) (16, 28, 29).

With ageing, from 20 years of age onwards, the concentration of 7-dehydrocholesterol in the epidermis decreases linearly over the lifespan. Therefore, the skin's capacity to produce vitamin D decreases and is reduced by approximately 75% by 70 years of age (17, 28).

A significant negative association between adiposity and low 25(OH)D in humans has also been suggested in recent research. Reasonable explanations for this include sun exposure avoidance and limited mobility in overweight people, clothing habits, volumetric dilution in a larger body volume, and decreased bioavailability of vitamin D circulating due to enhanced uptake by adipose tissue (30, 31).

Limited time outdoors can also significantly reduce the amount of UV radiation received by the individual and therefore limit the cutaneous production of vitamin D. Modern society structures have developed in a way that in most countries nowadays, the urban setting involves significantly higher amounts of time spent indoors rather than outdoors (13). That setting accounts for office-based working hours (usually during daylight hours) and a sedentary lifestyle that, besides reducing the amount of time outdoors compared to active peers, also includes a preference for private or public automotive vehicles rather than cycling or walking for routine transit. Moreover, it is not uncommon for sports training and physical activity to occur indoors (13). Several studies have also shown that older, hospitalised, or institutionalised populations are at a greater risk of having vitamin D inadequate levels due to the reduced or almost no time spent outdoors (32, 33).

Clothing habit due to cultural or religious preferences or to very cold weather is also an important influencing factor that may significantly reduce vitamin D synthesis (32, 33). Individuals who wear clothing covering most of the body have a greater risk of vitamin D deficiency as the area exposed to sunlight is significantly reduced (32).

In the Middle East and South Asia, despite abundant sunshine, probably due to a very traditional lifestyle which includes covering most parts of the body as a clothing style or due to extremely hot temperatures, a high prevalence of vitamin D deficiency has been reported (34, 35, 36, 37). A systematic review reported that the prevalence of vitamin D deficiency in the Middle East varies between 30 and 90% depending on the type of study, country, age group, and assay used (38).

Several studies have also repeatedly shown lower vitamin D status in black/Asian ethnic backgrounds and that vitamin D associations are different than in those from women from white ethnic background (39).

Industrialised and/or high traffic cities are likely to have considerable air pollution containing elevated amounts of ozone, efficiently absorbing UVB radiation (more specifically solar radiation below 290 nm), leading

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to less availability of UVB radiation reaching the skin (13, 16). Some studies suggest an association between air pollution levels and 25(OH)D status, where higher 25(OH)D concentrations are observed in populations in less polluted areas of a city (13, 16).

The paradox of vitamin D deficiency versus skin cancer

In contrast with the benefits of sensible casual exposure to sunlight, prolonged skin exposure to intense solar UV radiation can lead to acute and chronic health outcomes, including inflammatory effects, for the skin, eyes, and immune system (40, 41). In the long term, the acute effects of sunburn and tanning from excessive exposure to sunlight can provoke further degenerative alterations in cells and consequent premature skin ageing or the development of cancerous cells (40, 41, 42).

The UVB action spectrum for pre-vitamin D formation in the skin overlaps considerably with the spectrum for detrimental effects of sunburn (erythema); thus, sun avoidance to reduce the negative consequences of sunburn is likely to lead to a concomitant reduction in vitamin D synthesis (42). It has been recently proposed that pharmacologic high doses of vitamin D might have the ability to suppress the inflammation caused by UVR, although this was observed only in very few *in vitro*, animal, or *in vivo* small sample studies. Further investigation with robust randomised controlled trials (RCTs) is still required on this matter (43). Therefore, due to the complexity of guidance on sunlight exposure considering both vitamin D adequacy and risk of skin cancer, it is evident that recommendations must be latitude specific.

A guidance report from Food and Agriculture Organization/World Health Organization recommends that the most efficient physiological approach to acquiring vitamin D for populations at the equatorial latitude range (42°N–42°S) is through endogenous synthesis via sunlight exposure. The report specifically suggests that daily exposure of arms and face, without sunscreen, for approximately 30 min would be enough to maintain adequate vitamin D levels. Nonetheless, it also recognises the negative influence of several environmental and individual factors (such as latitude and season, ageing, skin pigmentation, clothing, and sunscreen use) on vitamin D production in the skin. Finally, the report recommendations for future research include a better understanding of the relationship between latitude, sun exposure, and vitamin D synthesis (44).

In the United States and Europe, it is generally recommended that exposure of arms and legs for 5–30 min between 10:00 h and 15:00 h twice a week would be enough for adequate levels, but taking into consideration time of day, season, and skin pigmentation (16).

In contrast, the increasing awareness of the higher risk of skin cancer related to direct sun exposure might adversely influence skin synthesis of vitamin D. Regular use of sunscreen, direct sun avoidance and 'covering up' are largely advised in sunny countries, particularly in countries with a high incidence of skin cancer like Australia and Brazil (45, 46).

For an adult with moderately fair skin pigmentation in Australia and New Zealand, it is recommended that unprotected exposure to sunlight for 5–10 min mid-morning or mid-afternoon during summer and 10–30 min midday during winter is sufficient to maintain adequate vitamin D levels for bone health purposes. For darker skin individuals, recommendations range from 15 to 60 min during summer and 20 min to 3 h during winter (45). In Brazil, there is no official guidance for sunlight exposure for the purpose of maintaining adequate vitamin D status. The Brazilian Society of Dermatology has very recently published a statement advising caution towards sunlight exposure due to the risks of skin cancer. This document advised that exposure to sunlight in Brazil should be minimised or avoided between 10:00 h and 15:00 h and recommended the use of protective clothing and hats as well as the frequent use of sunscreen on uncovered body areas when out in the sun, at any time of the day (46). Therefore, new studies are required to support recommendations for adequate sun exposure in tropical countries that consider both the risk of cancer and the maintenance of adequate vitamin D status.

Genetic factors

In addition to UVB radiation levels, recent studies suggest that genetic factors also largely influence serum 25(OH)D concentrations, and various genome-wide association studies have identified genes involved in the synthesis, metabolism, or transport of vitamin D (47, 48). An SNP in the VDR gene can affect the degree of genic expression, and thus the level of the protein (47). The extensive scope of vitamin D functions has brought great attention to the VDR gene as a key candidate gene in the attempt of explaining variations in specific phenotypes that might be linked with vitamin D metabolism (48).

Other SNPs have also been related to vitamin D metabolism, transport, and signalling pathways. For

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example, rs10741657 is a genetic variation in CYP2R1 that may cause impaired 25-hydroxylase activity with subsequent reduction in 25(OH)D synthesis. Other candidate SNPs that have been increasingly studied are rs6013897 in CYP27B1, rs6013897 in CYP24A1, and rs12785878 in DHCR7 (49, 50). The rs10783219 in the GC/DBP gene can affect the vitamin D binding protein, leading to a lower affinity with 25(OH)D3 and 1,25(OH)2D3, also resulting in low serum concentrations of 25(OH)D (49, 50, 51).

Thus, genetic variations could explain differences in vitamin D status and reduced levels of this vitamin even in individuals with adequate sun exposure or supplementation. However, the current evidence suggests that the genetic variation is small compared to the considerable variation in vitamin D status observed in different populations worldwide (10). This significant variability in vitamin D status can also be due to the availability of many different methods which poses a major challenge not only to the interpretation and comparison of different data sets but particularly to the development of international evidence-based recommendations (14, 15).

Optimal vitamin D status

The metabolite 25(OH)D is the major circulating form of vitamin D, with a half-life of approximately 2–3 weeks and excellent stability. It reflects vitamin D from both dietary intake and photochemically production in the skin (11, 52). Therefore, it is universally accepted as the best indicator of vitamin D status (52, 53). The active form 1α,25-dihydroxyvitamin D or 1,25(OH)$_2$D is chemically unstable and has a half-life of a few hours and, therefore, is not recommended as an indicator of vitamin D status (52, 53).

Circulating 25(OH)D can be measured by several methods, including immunoassays, protein binding assays, high-performance liquid chromatography (HPLC), and liquid chromatography-tandem mass spectrometry (LC-MS/MS) (15, 52, 53). This variety of methods may partially explain the variability of results. However, there is a consensus that 25(OH)D assays should detect both metabolites 25(OH)D$_2$ and 25(OH)D$_3$ and that HPLC and LC-MS/MS methods are the gold standard for 25(OH)D measurement (14, 15, 53).

Moreover, evidence has shown significant differences even in the same laboratory as inter-assay variations in standard procedures may lead to very different results. The Vitamin D External Quality Assessment Scheme, established in 1989, has significantly helped to improve assay performance and development via external control of accuracy (14). In 2010, the National Institute of Health Office of Dietary Supplements, together with the Centers for Disease Control and Prevention, National Centre for Environmental Health, National Institute of Standards and Technology, and Ghent University, proposed the Vitamin D Standardisation Program (VDSP). The main objective of VDSP is to increase the comparability of data from different national surveys around the world (14).

Although protocols for standardisation of 25(OH)D data are a relevant facilitator of cross-population comparisons, a few other critical aspects should also be considered in assessing vitamin D status. Individual variation might be influenced by the month the samples are collected. Results may over or underestimate 'true' values due to confounders such as holidays to a sunnier/colder location during the sampling period, vitamin D supplement intake, medication, or medical treatment likely to affect vitamin D metabolism or use of sunbeds (14, 32, 33).

There are still ample discussions and controversies about serum 25(OH)D concentrations that should be considered deficient, insufficient, and sufficient (10, 54). The most common criteria used for determining the optimal serum 25(OH)D concentration for bone health in adults include the suppression of parathyroid hormone secretion, higher bone mineral density, reduced rates of bone loss, and decreases in fractures and falls (10, 54). There is a general comprehension that circulating 25(OH)D concentrations of populations should not fall below 25 nmol/L at all ages to preserve bone health (10, 53, 55, 56). However, there is an emerging consensus for a threshold much higher than this is required to maintain skeletal health and improve overall health and well-being (57, 58). For instance, the Institute of Medicine defines insufficiency as 25(OH)D concentrations below 50 nmol/L (53) and the US Endocrine Society proposes 75 nmol/L as the minimum level required to prevent detrimental effects to health (40).

Vitamin D metabolism

Vitamin D is a misnomer as it is not actually a vital amine but a pro-hormone, required throughout life. Several tissues and cells in the human body express CYP27B1 and therefore are potentially capable of converting 25(OH)D to the active form, 1,25-dihydroxyvitamin D3 (1α,25(OH)2D3) including several key peripheral sites, such as the immune system and skin. Furthermore, the production of 1,25(OH)2D in extra-renal cells is regulated differently from the kidney, raising the question of whether

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non-renal cells produce 1,25(OH)2D for their specific necessities at a local level (3, 16, 59, 60).

The primary physiologic function of vitamin D and its metabolites is maintaining calcium homeostasis for metabolic functioning, signal transduction, and neuromuscular activity. The biologically active metabolite $1\alpha,25(OH)_2D_3$ is involved in bone formation and maturation (3, 55). Along with parathyroid hormone (PTH), it regulates calcium and phosphorous metabolism and enhances the absorption of calcium in the gut and reabsorption of filtered calcium in the kidney. $1\alpha,25(OH)_2D_3$ is the only known hormone to induce the proteins involved in active intestinal calcium absorption (12, 55).

When calcium concentrations decrease below normal physiologic levels, calcium-sensing proteins stimulate PTH secretion and the expression of the PTH gene to restore calcium homeostasis. Consequently, the active $1\alpha,25(OH)_2D_3$ hormone stimulates intestinal calcium absorption or, along with PTH, in the case of higher concentrations of the latter, increases the mobilisation of calcium from the bone and renal calcium reabsorption (12, 55). If calcium concentrations exceed normal physiological concentrations, C-cells in the thyroid gland release calcitonin to suppress calcium mobilisation from bone. Low serum 25(OH)D concentrations have been associated with significantly higher serum PTH and higher serum 1,25(OH)2D, suggesting that the PTH is likely regulated by 25(OH)D with a stimulating effect of PTH on the enzyme 25-hydroxyvitamin D 1α-hydroxylase to counteract the deficiency of the substrate 25(OH)D (61, 62).

With low vitamin D concentrations, calcium and phosphorus absorption in the small intestine are reduced to 10–15% and 60%, respectively. In contrast, with higher vitamin D concentrations, intestinal absorption can increase up to 30–40% for calcium and 80% for phosphorus (3, 55).

Vitamin D and musculoskeletal health

Vitamin D enhances calcium absorption, bone mineralisation, promotes maintenance of muscle function, and is crucial for musculoskeletal health. Low vitamin D status triggers secondary hyperparathyroidism, increases bone loss, and leads to muscle weakness. Observational studies show that lower serum concentrations of 25(OH)D are associated with higher risks of falls and fractures (56).

Over more than a decade now, systematic reviews with meta-analysis have shown that both calcium and vitamin D in sufficient amounts are required to achieve a reduction in fractures, supported by several subsequent RCTs and further meta-analysis updates. Most meta-analyses have examined the effect of vitamin D on BMD and fracture incidence (62, 63, 64, 65, 66, 67), although presenting some varying outcomes. Overall, it has been evidenced that the effect of vitamin D is greater in the elderly (>70 years) and individuals in a residential care setting compared to independent living (10, 64). Also, there seems to be a greater effect with a minimum daily dose of 800 IU and in individuals with low baseline serum 25(OH)D (10, 54, 68). There have been consistent reports that the observed effects of preventing hip fracture or any new fracture apply to vitamin D combined with adequate calcium intake but not vitamin D supplementation alone (10, 63, 64, 66, 67, 69, 70). Based on this mounting evidence, supplementation with 800 IU of vitamin D per day, combined with 1200 mg of calcium per day, has been recommended to prevent fractures and falls in older adults, particularly in individuals with low vitamin D status and those institutionalised (53, 64, 71).

In a case–control study with 600 female Navy recruits who were diagnosed subsequently with a stress fracture of the tibia or fibula and 600 matched controls who did not experience a stress fracture, there was double the risk of stress fractures of the tibia and fibula in women with serum 25(OH)D concentrations of less than 50 mol/L compared to those with concentrations of 100 mol/L or greater (72).

In addition, the Hertfordshire Cohort Study (n =820), an established longitudinal cohort study of community-dwelling adults, recruited 820 participants, which were seen at baseline and 9–12 years later for a follow-up (n =339). There was an association between serum 25(OH)D concentrations and hip BMD in men, but there were no associations with hip BMD in women. The population in this study was exclusively European Caucasian and there was no information regarding the amount, duration, and compliance of vitamin D supplementation and no information regarding physical activity spent indoors or outdoors (73).

There have been some conflicting results reported from RCTs and meta-analyses of vitamin D alone but also in combination with calcium for the prevention of fracture and falls both in community-dwelling elders and the general population. Some suggested protective effects and others demonstrated no beneficial effects (64, 65, 66, 67, 71, 72, 74, 75). Nevertheless, several considerations around the data presented in some vitamin D supplementation studies would need to be borne in mind (10, 54).

First, most studies still neglect the influence of participants with adequate vitamin D status at the

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beginning of the trial, which would not obtain the expected benefits from supplementation. In addition, not all RCTs were entirely comparable regarding study design and protocol mainly due to a combination of small sample size with insufficient statistical power, different doses of vitamin D, dosing regimens (daily or monthly), duration of treatment (most were less than 1 year), and poor compliance. Furthermore, interpretation of the results might be influenced by failure to report baseline or achieved differences in serum 25(OH)D concentrations and the season of data collection.

Another finding that has provoked discussion among researchers is from a meta-analysis that investigated the effect of vitamin D supplementation on fractures, falls, and bone density by examining trials that compared vitamin D with untreated controls, placebo, or lower-dose vitamin D supplements (76). The analysis also included trials with multiple interventions (e.g. co-administered calcium and vitamin D) if the study groups differed only by use of vitamin D. The authors concluded that 'vitamin D supplementation does not prevent fractures or falls, or has clinically meaningful effects on bone mineral density', with no differences between the effects of higher and lower doses of vitamin D, and therefore there would be 'little justification to use vitamin D supplements to maintain or improve musculoskeletal health'. These findings and conclusions have provoked much debate among experts, particularly concerning some relevant aspects of the analysis conducted (10, 54): the analysis excluded all studies comparing calcium plus vitamin D and double placebo; 60% of the studies had a duration of less than 1 year (considered not enough time to observe beneficial effects of antiosteoporosis nutrients on fracture risk); in 40% of the included studies, mean serum 25(OH)D at baseline was above 50 nmol/L (sufficiency threshold and therefore not expected to show significant benefits to bone health); and only 2% of the overall population analysed had 25(OH)D below 30 nmol/L (critical threshold where significant improvements to bone health are likely). Moreover, it has been pointed out that the analysis included studies with high intermittent boluses of vitamin D and the trial with individuals at the highest fracture risk reported poor compliance of around 50%. Although there is still a lack of consensus regarding these relevant aspects, considering the amount of robust evidence of the role of vitamin D on important musculoskeletal outcomes, supplementation strategies, and sun exposure recommendations should not be dismissed.

It is worth noting that poor RCT design and data collection may account for vitamin D trials that have failed to find beneficial effects from supplementation. Heaney (2014) proposes that the minimum requirements for optimising the design and analysis of clinical studies of nutrient effects should include the measurement of basal nutrient status (and considered as an inclusion criterion); large enough intervention (i.e. change in nutrient exposure or intake) to change nutrient status which must be quantified by suitable analyses; measurement and recording of the change in nutrient status produced; the hypothesis to be tested must be that a change in nutrient status (not just a change in diet) produces the sought-for effect; and optimised co-nutrient status in order to ensure that the test nutrient is the only nutrition-related, limiting factor in the response. Additionally, studies must start from the same or similar basal nutrient status value, use the same or closely similar doses, use the same chemical form of the nutrient or same food matrix, have the same co-nutrient status, and have approximately equal periods of exposure to the altered intake (77).

Since most trials so far did not select participants with deficient serum 25(OH)D concentrations at baseline, the magnitude of the effect of vitamin D and its metabolites on bone mineral density, bone turnover, and fracture or fall incidence is still not completely clear. Noteworthy is the need for study designs that appropriately consider the effects of vitamin D supplementation according to age, sex, latitude, vitamin D supplement dose, the combination of dietary calcium intake and supplements, and the presence of single nucleotide polymorphism in genes associated with vitamin D metabolism.

In addition to the action on the prevention of fractures and falls, researchers have sought to investigate the influence of vitamin D levels on physical performance and injury (78, 79, 80, 81). The main hypothesis is that a low level of serum vitamin D might directly affect muscle strength and performance. Studies in non-athlete young people and the elderly reported low 25(OH)D concentrations negatively associated with muscle strength markers (82, 83). Several observational studies report an association of low serum vitamin D levels (<80 nmol/L) with reduced muscle strength, musculoskeletal injuries, and infections (80) and even affecting the training efficiency of young athletes (79).

In addition, a recent systematic review and meta-analysis of RCTs in postmenopausal women has summarised the effects of vitamin D supplementation (with or without calcium) on measures of muscle strength and mobility. The study suggests that vitamin D supplementation does not affect mobility, though there was a minor improvement in muscle strength after

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receiving vitamin D supplements compared to control groups, with a greater improvement with doses > 1000 IU per day, a trial duration of at least 3 months and baseline vitamin D concentrations below 75 nmol/L. The authors report a high degree of heterogeneity and studies performed on subjects with different health statuses (i.e. subjects with obesity, type 2 diabetes, osteoporosis, and osteopenia, as well as those who were healthy). They also highlight heterogeneity in dose, duration, and form of vitamin D supplements and methods used for the measurement of functional performance.

A recent meta-analysis sought to evaluate the association between vitamin D status and sport injuries. The review included seven studies investigating stress fractures and nine investigating musculoskeletal injuries. Serum vitamin D concentrations below 75 nmol/L seemed to be associated with an increased risk of stress fractures and there was an increased odds ratio for stress fracture with vitamin D insufficiency. Only two studies reported that low serum vitamin D concentrations were associated with musculoskeletal injuries. A heterogeneous definition and reporting of musculoskeletal injuries may have influenced the results (84).

Recent studies have also started to show new robust evidence on the beneficial effects of vitamin D supplementation beyond musculoskeletal health, such as type 2 diabetes, cancer, and cardiovascular disease. (85, 86).

Risk of toxicity

Vitamin D metabolism is tightly autoregulated and responds promptly to excessive endogenous vitamin D production via exposure of the skin to sunlight, which could lead to severe toxicity and potentially hypercalcemia, causing renal failure and cardiac arrest (10, 16). With continuous exposure to sun radiation, pre-vitamin D_3 and vitamin D_3 in the epidermis are degraded into biologically inactive photoproducts (12, 16). For instance, an *in vitro* study conducted in Boston, with neonatal foreskins, showed a photodegradation of 30% of vitamin D after 10 min of sunlight exposure and as much as 95% after 3 h of exposure (87).

Nevertheless, vitamin D intake in high doses may cause severe toxicity and can potentially lead to hypercalcemia with consequent renal failure and cardiac arrest (12). The concentration associated with hypercalcemia has been estimated to be 250 nmol/L (10, 12). To this date, no adverse effects or toxicity cases have been reported in trials with adults receiving up to 10,000 IU of vitamin D_3 daily (88). In 2010, the Institute of Medicine doubled its recommendation for a tolerable upper limit of vitamin D, which was increased from 2000 to 4000 IU per day (53).

A paper published in 2019 reported that a psychiatric hospital offered its patients daily vitamin D supplementation since 2011 to treat or prevent vitamin D deficiency. The hospital has admitted over 4700 patients, of which the vast majority received either 5000 or 10,000 IU/day (attending doctor's choice), with a few receiving larger amounts, ranging from 20,000 to 50,000 IU/day according to specific disease concerns. The authors report that 'there have been no cases of vitamin D3 induced hypercalcemia or any adverse events attributable to vitamin D3 supplementation in any patient' (89).

Conclusions

Vitamin D plays a crucial role in bone health. A considerable amount of human evidence supports the well-recognised contribution of adequate serum 25(OH)D concentrations for bone homeostasis maintenance and prevention and treatment strategies for osteoporosis when combined with adequate calcium intake.

There is a clear need for consistent data to establish realistic and meaningful recommendations of vitamin D status, particularly for different population groups. Although the literature is unanimous on the essential role of vitamin D on calcium homeostasis and bone health, there is still a lack of consensus on critical points such as optimal thresholds for vitamin D deficiency as well as toxicity, optimal intake of vitamin D, vitamin D supplement as a strategy to prevent fractures and falls, recommended sun exposure at different latitudes for different skin pigmentations, and the extraskeletal effects of vitamin D.

The public health recommendations and messages around adequate sunlight exposure and vitamin D intakes (whether by diet or supplements) are currently confusing for most people. Moreover, they do not consider important, influential factors such as ethnicity and skin pigmentation, cultural behaviour, lifestyle, the latitude of residence, and season of the year. Additionally, a lack of consensus on desirable 25(OH)D concentrations worldwide means it is difficult to recommend a vitamin D intake required to achieve an optimal level, again further confounded by potential ethnic differences in metabolism between different population groups. Another barrier to achieving consensus on optimal levels and subsequent lifestyle recommendations is the impossibility of making direct comparisons between trials due to relevant differences in

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methodological design and populations. Thus, it is not appropriate to extrapolate study findings from countries located in different latitudes with different cultural habits, availability of vitamin D food sources, skin pigmentation spectrums, and lifestyle.

A better understanding of the actual unique contributions from vitamin D dietary intake (from food and supplements) and sunlight exposure, along with influential factors, on serum vitamin D concentrations and consequent clinical outcomes, will significantly contribute to the determination of meaningful and context-specific recommendations for different populations. Subsequently, such knowledge will be key in determining public health strategies and policies for efficient prevention and treatment of vitamin D inadequacy.

However, the current consensus is that sun exposure at adequate time and/or vitamin D supplementation should be recommended in all institutionalised and frail elderly as well as in individuals with serum 25(OH)D concentrations below 25 nmol/L. There is also a growing consensus that subjects with limited exposure to sunlight are very likely to require vitamin D supplementation to maintain adequate serum 25(OH)D concentrations.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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