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Vitamin D in adolescents: Are current recommendations enough?☆

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ABSTRACT

Vitamin D is essential for bone development during adolescence and low vitamin D status during this critical period of growth may impact bone mineralization, potentially reducing peak bone mass and consequently increasing the risk of osteoporosis in adulthood. Therefore, the high prevalence of vitamin D inadequacy and deficiency in adolescent populations is of great concern. However, there is currently a lack of consensus on the 25-hydroxyvitamin D [25(OH)D] concentration, the widely accepted biomarker of vitamin D status, that defines adequacy, and the vitamin D intake requirements to maintain various 25 (OH)D thresholds are not well established. While the current intake recommendations of 10–15 μg/day may be sufficient to prevent vitamin D deficiency (25(OH)D < 25–30 nmol/l), greater intakes may be needed to achieve the higher threshold levels proposed to represent adequacy (25(OH)D > 50 nmol/l). This review will address these concerns and consider if the current dietary recommendations for vitamin D in adolescents are sufficient.

1. Introduction

Vitamin D insufficiency is widely recognised as a global public health concern, and can affect all population groups irrespective of gender, age or ethnicity. More severe and prolonged vitamin D deficiency can result in rickets in children and osteomalacia in adults [1,2]. Adolescence is a critical period of growth and bone development, and less severe vitamin D insufficiency may prevent adolescents achieving peak bone mass [3,4]. Given the important and well-recognized role of vitamin D in calcium absorption and bone health, it is therefore concerning that low vitamin D status is prevalent among adolescents worldwide [5]. Despite this, adolescents appear to be a somewhat neglected population group with a limited evidence base for setting vitamin D intake requirements, with those that exist extrapolated from adult data, which may not always be appropriate. This review will consider firstly the definitions of optimal vitamin D status in adolescents, and secondly whether the current dietary intake recommendations are adequate to achieve this, given the high prevalence of low vitamin D status in this vulnerable population group.

2. Sources of vitamin D

Vitamin D is a unique nutrient in that the main source is sun exposure, rather than diet. The majority of vitamin D is synthesized within the human body via the action of ultraviolet B (UVB) radiation on the skin, which mediates the conversion of 7-dehydrocholesterol, a cholesterol precursor present within the skin, to vitamin D_3. Vitamin D_3 then undergoes two hydroxylation steps, first in the liver to the biologically inactive form, 25-hydroxyvitamin D [25(OH)D], and secondly in the kidneys to the active 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] [6].

The amount of vitamin D_3 synthesized within the skin is a function of the amount of UVB radiation reaching the skin and the availability of 7-dehydrocholesterol within the epidermis. Consequently the level of vitamin D_3 synthesis is dependent on a number of environmental and individual factors, including latitude, season, ethnicity, clothing that completely covers the skin for cultural or religious beliefs, use of sunscreen, time spent outdoors, obesity and aging [7]. During the winter-time at northerly latitudes, the increasing zenith angle of the sun results in little, if any, cutaneous synthesis of vitamin D_3. Therefore, during times of insufficient sun exposure, dietary sources of vitamin D become important in maintaining vitamin D status. However, this proves to be challenging as there are few foods that are a naturally rich source

Abbreviations: BMD, bone mineral density; DBP, vitamin D binding protein; IOM, institute of Medicine; PTH, parathyroid hormone; UVB, ultraviolet B; 1,25$(OH)_2$D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D.

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of vitamin D [6] and there is increasing evidence to suggest that current vitamin D intakes are inadequate to compensate for the seasonal deficit in sunlight during the winter-time. While food fortification and supplement use can be effective in increasing dietary intakes of vitamin D, fortification policies currently vary dramatically between countries and often occur on a voluntary basis, while uptake and adherence to supplement use varies by gender and age group [8].

Several studies have reported inadequate dietary vitamin D intakes among adolescents, although this varies by country due to dietary habits, fortification policies and supplement use. In the European Nutrition and Health Report, vitamin D intakes ranged from 1.5–7.5 μg/day in 13–24 year old males and females [9]. The lowest intakes were seen among Spanish adolescents (1.8 and 1.5 μg/day in male and female 15–18 year olds respectively), closely followed by Austrian males and British females at 2.0 μg/day. Intakes were below 5 μg/day in all sub-groups except for Polish males (5.5 μg/day) and Norwegian males and females (15–18 years), who had the highest intakes at 7.5 and 7.1 μg/day respectively. This could be attributed to high consumption of fish and supplement use, as Norway, like much of Europe, has limited vitamin D fortification of foods [8,10]. The exception to this is Finland, who since 2003 have fortified fluid milks, margarines and spreads. While this policy increased dietary vitamin D intakes in 4 year old children [11], supporting the assertion that fortified milk is a major determinant of 25(OH)D status in young children [12], it had little impact on the vitamin D intakes of 12–18 year old adolescent females, with no change in 25(OH)D concentrations [13]. This is likely due to low consumption of dairy products in adolescent females, demonstrating the importance of giving consideration to food consumption patterns when developing fortification policies. Furthermore, this may also be influenced by ethnic differences in dietary patterns, with African American adolescent females reported to consume more vitamin D from meat and bean food sources compared to white females who consumed more from milk [14]. Fortification is also more commonly practiced in the United States compared with Europe. Using data from the National Health Nutrition and Examination Survey (NHANES) 2003–2006, Fulgoni et al. reported intakes of 1.7 μg/day in 2–18 year olds from naturally occurring food sources of vitamin D, which increased to 6.1 μg/day when fortified foods were also included [15]. When supplement use was also considered, intakes increased to 8.3 μg/day. While supplements can increase intakes of vitamin D, uptake tends to be lower in adolescents compared with younger children [16], so perhaps may not be the most appropriate strategy for improving vitamin D intakes in the adolescent population.

3. Defining vitamin D deficiency and adequacy and selected outcome measures

3.1. Vitamin D deficiency and rickets

Circulating 25(OH)D concentration serves as the best indicator of vitamin D status as it reflects both dietary intakes and cutaneous synthesis of vitamin D and has a long half-life of 2–3 weeks. Measurement of $1,25(OH)_2D$ is not considered useful for assessment of vitamin D due to its short half-life (4–7 h) and its tight homeostatic regulation [17].

There is generally good agreement that populations should not have 25(OH)D concentrations of less than 25–30 nmol/l based on an increased risk of rickets and impaired bone growth [18]. Vitamin D deficiency rickets remains a public health concern among infants particularly in communities in Asia, Africa and the Middle East, due to a high prevalence of low vitamin D status during pregnancy, breast feeding and breast milk that is low in vitamin D, darker skin pigmentation and cultural dress [1]. However it is important to recognise that rickets can also occur during childhood and adolescence, which is attributable to insufficient dietary calcium intakes. Children presenting with rickets in South Africa and Nigeria were found to have low intakes of dairy products and diets high in unrefined cereals and phytate, which impairs calcium absorption [19,20]. In a 24-week randomized trial of 4 year old Nigerian children with rickets and low habitual dietary calcium intakes (~200 mg/day), supplementation with calcium alone (1000 mg/day) and calcium in combination with vitamin D (1000 mg/day calcium and 1500 μg vitamin D administered at baseline and 12 weeks) were found to be equally effective in treating rickets and more so than vitamin D treatment alone [21]. The mean serum 25(OH)D concentration of these children at baseline was 35 ± 25 nmol/l, with 37% having concentrations below 30 nmol/l. At the end of the intervention serum 25(OH)D concentrations were 52, 87 and 102 nmol/l in the calcium alone, vitamin D alone and calcium plus vitamin D groups [21].

3.2. Defining vitamin D adequacy and measures of bone health

There is much debate and controversy surrounding which levels of circulating 25(OH)D should be considered as adequate or 'optimal'. At present, the Institute of Medicine (IOM) [18], European Food Safety Authority (EFSA) [22], American Academy of Pediatrics [23] and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition [24], among others, suggest a serum 25(OH)D concentration of >50 nmol/l as being adequate. However others have proposed much greater 25(OH)D sufficiency thresholds. The Endocrine Society [25] and The Society for Adolescent Health and Medicine [26] for example, consider sufficiency at 25(OH)D concentrations >75 nmol/l, and deficiency below 50 nmol/l. These cut-off thresholds are often based on data from adult studies that use various biochemical and/or functional outcome criteria to define vitamin D adequacy, such as suppression of parathyroid hormone (PTH), maximal calcium absorption and bone mineral density. However it is important to note that it may not always be appropriate to use such criteria for the adolescent population. A good example of this is the relationship between vitamin D and PTH. While it is well established that vitamin D deficiency in elderly subjects leads to increases in PTH and consequently increased bone turnover and bone loss [27], the elevated PTH concentrations observed in adolescents may not necessarily be detrimental to bone health when the rate of bone modelling, skeletal growth and bone consolidation are at a peak [28,29]. Adolescent studies have failed to identify a consistent inflection point for maximal suppression of PTH and this therefore brings into question the use of such a criteria in defining vitamin D adequacy in adolescents [3,30–33]. Furthermore, it has been suggested that increasing 25(OH)D concentrations in adults may enhance calcium absorption, although studies in adolescents have shown that 25(OH)D concentrations above ~30–50 nmol/l are not associated with any increased benefits with respect to calcium absorption [34–36].

A review of data linking vitamin D status to various health outcomes indicated that 25(OH)D concentrations of 90–100 nmol/l were optimal in relation to bone mineral density, fracture prevention, lower extremity function and colorectal cancer in adult populations [37]. Studies evaluating vitamin D status and bone mineralization in the adolescent age group have reported unfavourable effects of circulating 25(OH)D concentrations of less than 40 nmol/l on bone mineral density (BMD) of various skeletal sites. In particular, studies in Finnish females reported that those with 25(OH)D concentrations <40 nmol/l had lower BMD of the radius and ulnar [3], whilst reduced lumbar spine BMD was

demonstrated in those with 25(OH)D concentrations below 37.5 nmol/l [4]. This is also supported by the study of Viljakainen et al. in which bone mineral accretion of the femur was 14.3% and 17.2% greater in 11–12 year old Finnish females receiving 5 and 10 μg/day vitamin D respectively, compared with those in the placebo group [38]. The authors concluded that positive effects on bone mineral accretion were seen when serum 25(OH)D concentrations were >50 nmol/l. A Cochrane systematic review of vitamin D supplementation and BMD in children and adolescents found no improvement in BMD following vitamin D supplementation in those with adequate 25(OH)D concentrations, although suggested that supplementation may benefit those with lower 25(OH)D concentrations (<35 nmol/l) [39].

Therefore, at this time, there is little evidence to suggest that higher 25(OH)D concentrations (>90 nmol/l) are beneficial in adolescents and further studies are needed to help identify the 25(OH)D concentration for optimal bone health within this age group. Regarding non-bone health outcomes, the evidence in adolescent populations is extremely limited and some argue that proposals for higher 25(OH)D concentrations >75 nmol/l are premature given the lack of robust data from randomized controlled trials regarding these functional outcomes [18,40].

Vitamin D status is traditionally determined via the measurement of circulating 25(OH)D concentrations. Vitamin D binding protein (DBP), the main carrier protein responsible for transporting 25(OH)D to target cells, binds to 85–90% of total circulating 25(OH)D, with a further 10–15% bound to albumin and less than 1% in the free form [41]. The 'free hormone' hypothesis proposes that the unbound or free fraction of the hormone is responsible for its biological activity rather than the protein bound fraction [42] and so free 25(OH)D may enter the cells more readily and be converted to the active $1,25(OH)_2D$ [43]. Recently studies have attempted to measure free 25(OH)D concentrations, either by direct measurement or by indirect estimation based on the measurement of DBP, albumin and 25(OH)D [44–47]. Concentrations of free 25(OH)D are dependent on DBP concentrations and genetic polymorphisms of DBP that differ in their binding affinity for vitamin D, which vary depending on ethnic background: African American populations are more likely to carry the higher affinity DBP genotype, while white Caucasian populations more frequently carry the lower affinity genotypes [48]. Population studies have reported that although total 25(OH)D concentrations were lower among African American compared to white Caucasian population groups, free or bioavailable 25(OH)D (free and albumin bound 25(OH)D) concentrations were comparable between the populations, leading authors to suggest black African Americans may be incorrectly identified as being vitamin D deficient based on total 25(OH)D concentrations alone [44,45]. This may explain why African American populations commonly demonstrate greater bone mass and lower fracture rates than their white Caucasian counterparts despite the lower 25(OH)D concentrations [49,50]. Free and bioavailable 25(OH)D was found to be strongly associated with lumbar spine BMD in healthy adults after adjusting for sex, age body mass index and race, while total 25(OH)D concentrations were not associated with BMD, lending support to the free hormone hypothesis [46]. Additionally, DBP genotypes were found to influence 25(OH)D and PTH concentrations and BMD in Finnish adolescents, suggesting DBP may affect bone mass accrual during adolescence [51]. These data suggest measurement of free or bioavailable 25(OH)D may be a good measure of vitamin D activity in relation to bone health, and may in the future help further elucidate the relationship between vitamin D and non-musculoskeletal health outcomes. However, it remains to be determined if free 25(OH)D will be a better biomarker of vitamin D status and

Table 1
Prevalence of vitamin D deficiency and inadequacy among adolescents worldwide.

Country (latitude)	Season	Age (yrs)	Prevalence of 25(OH)D deficiency and inadequacy (%)		Reference
			<30 nmol/l	<50 nmol/l	
Europe (HELENA)	Year round	12.5–17.5	15[a]	27[b]	[52]
United Kingdom (50–59°N)	Year round	4–18		35	[53]
United Kingdom (NDNS)	Winter	11–18	40[c]		[54]
Northern Ireland (55°N)	Winter	12 & 15		46	[55]
Norway (69°N)	Year round	15–18	17[c]	60	[56]
USA (42°N)	Winter	9–14		83	[57]
USA (NHANES 01-06)	Year round	16–19	6[c]	33	[58]
Canada (CHMS 07-09)	Year round	12–19	4	19	[59]
China (40°N)	Winter	15	33[c]	89	[60]
Korea (KNHANES 08-09)	Year round	10–18	13[a]	55[b]	[61]
India (28°N)	Summer	6–18	30[d]	91	[62]
Brazil (25–30°S)	Year round	7–18		36	[63]
United Arab Emirates (24°N)	Winter	15–18	20[e]	45	[64]
Saudi Arabia (21°N)	Winter	12–15	81[c]		[65]

HELENA, Healthy Lifestyle in Europe by Nutrition in Adolescence; NDNS, National Diet and Nutrition Survey; NHANES, National Health and Nutrition Examination Survey; CHMS, Canadian Health Measures Survey; KNHANES, Korea National Health and Nutrition Examination Survey.

[a] <27.5 nmol/l.
[b] ≥27.5–< 50 nmol/l.
[c] <25 nmol/l.
[d] <22.4 nmol/l.
[e] <37.5 nmol/l.

although this warrants further investigation, at present the measurement of total circulating 25(OH)D should continue to be the preferred biomarker of vitamin D status [45].

4. Prevalence of low vitamin D status in adolescent populations

Several studies have reported the prevalence of low vitamin D status among adolescents (Table 1), highlighting the truly global nature of vitamin D inadequacy and indeed deficiency. As can be seen in Table 1, from a selection of recent nationally representative or individual studies, the prevalence of vitamin D inadequacy (25(OH)D <50 nmol/l) ranged from 19 to 91% of adolescents worldwide, while the prevalence of deficiency (25(OH)D < 22.4–30 nmol/l) ranged between 4% and 81%.

However, it is important to take into consideration the difficulties in comparing data from different studies due to variations in subject characteristics, including age range, gender, ethnicity and cultural dress, and in particular the latitude and season of sampling. Additionally, differences in analytical methods and assays used to measure 25(OH)D concentrations can further complicate the situation. A recent study aimed to estimate the prevalence of vitamin D deficiency across Europe through the application of the Vitamin D Standardization Program protocol to serum 25(OH)D from representative European data ($n = 55,844$) [66]. Biobanked sera were re-analysed using liquid chromatography-tandem mass spectrometry and prevalence estimates were generated using standardized 25(OH)D data. Overall, 13% of European individuals were estimated to have serum 25(OH)D concentrations <30 nmol/l (18% and 8% in winter and summer respectively). If a 25(OH)D threshold concentration of 50 nmol/l was considered, 40% had an inadequate vitamin D status. Perhaps most strikingly, adolescents aged between 15 and 18 years were found to have on average the greatest risk of vitamin D deficiency compared with younger children and adults. It is unclear what the reasons are which underlie this apparent increased risk and higher prevalence of vitamin D inadequacy and deficiency in adolescents, although negative associations between pubertal status and circulating 25(OH)D concentrations have previously been reported [34,67,68]. Furthermore, during puberty, the metabolism of 25(OH)D to 1,25$(OH)_2$D is increased, in order to enhance the efficiency of calcium absorption to satisfy the growing skeleton's requirements during this phase of rapid development [69]. However, it is not known if this has an effect on the vitamin D requirements of this age group.

5. Current recommendations

Many countries and international authoritative organisations have established vitamin D intake recommendations and some have recently been re-revaluated and revised. Due to difficulties in establishing the contribution of UVB exposure to vitamin D status, recommendations are often set assuming minimal sun exposure, and are generally established as the average daily intakes needed to meet the requirements of the majority of the population (i.e. the vitamin D intake needed to maintain 25(OH)D concentrations above the defined level of adequacy in 97.5% of the population). Additionally, they are based upon musculoskeletal health outcomes only, as there is currently insufficient evidence to set recommendations based on the risk of other health outcomes, such as cancer, cardiovascular disease or autoimmune diseases [18]. As demonstrated in Table 2, there is currently a lack of consensus on the intakes required to maintain 25(OH)D concentrations above differing levels of defined adequacy. While re-evaluating vitamin D recommendations, the IOM highlighted difficulties in establishing intake requirements for children and adolescents due to a lack of dose-response studies in younger subjects [18]. Proposed recommendations in children and adolescents are often extrapolated from adult data, which as previously discussed, may not always be appropriate. Dose-response randomized controlled trials are needed in the adolescent population to help establish the intake of vitamin D required to maintain adequate circulating 25(OH)D concentrations and the levels which are desirable for optimal bone health. While commonly recommended intakes of 10–15 μg/day may help avoid vitamin D deficiency during times of minimal sun exposure, it is unclear if these doses would maintain adequate vitamin D concentrations (i.e. 25(OH)D >50 nmol/l) and higher intake requirements may be needed.

6. Vitamin D intervention studies in adolescents

Intervention studies conducted in adolescents have demonstrated that vitamin D intakes of between 20 and 50 μg/day have

Table 2
Dietary intake recommendations for vitamin D (μg/day) by life stage as proposed by various authoritative organisations to maintain adequate serum 25(OH)D concentrations.

Organisation	Year	Country/ Countries	Recommended Dietary Vitamin D Intake (μg/d)						25(OH)D Adequacy Threshold (nmol/l)
			0–12 months	1–<4 yr	4–18 yr	19–69 yr	>70yr	Pregnancy/ Lactation	
European Food Safety Authority (EFSA) [22]	2016	Europe	10	15	15	15	15	15	50
Scientific Advisory Committee on Nutrition (SACN) [70]	2016	United Kingdom	8.5–10	10	10	10	10	10	25
Nordic Nutrition Recommendations [71]	2012	Denmark, Finland, Iceland, Norway, Sweden	10	10	10	10	20	10	50
German Nutrition Society [72]	2012	Germany, Austria, Switzerland	10	20[a]	20[a]	20[a]	20[a]	20[a]	50
Health Council of the Netherlands [73]	2012	The Netherlands	10	10	10	10	20	10	30[b]
Bone and Mineral Society, Endocrine Society and Osteoporosis Australia [74]	2012	Australia and New Zealand	15	15	15	15	20	15	50
Institute of Medicine (IOM) [18]	2011	North America and Canada	10	15	15	15	20	15	50
WHO/FAO Joint Expert Consultation [75]	2004	Worldwide	5	5	5	5–10	15	5	27
Other									
The Endocrine Society[c] [25]	2011	Worldwide	10 25	15 25	15 25	15–20 37.5–50	20 37.5–50	15 37.5–50	50 75

WHO/FAO, World Health Organization/Food and Agriculture Organization.
[a] Estimated value of adequate vitamin D intake with missing endogenous synthesis.
[b] Target concentration of 50 nmol/l for those aged >70 years.
[c] Recommendations for populations at risk of vitamin D deficiency.

achieved adequate 25(OH)D concentrations of ≥50 nmol/l, although very few of these have been dose-response studies. Based on dose-response studies in 11–12 year old white Finnish and Danish females and 14–18 year old white male and female adolescents in the UK, it was estimated that vitamin D intakes of 8.3 and 10.1 μg/day respectively would maintain serum 25(OH)D concentrations above 25 nmol/l during the winter-time in 97.5% of the population, thereby avoiding vitamin D deficiency [76,77]. Daily intakes of 18.6 and ~30 μg were estimated to ensure vitamin D adequacy (25(OH)D >50 nmol/l) in the majority (97.5%) of the younger and older adolescent populations respectively. However a further study in 9–15 year old Finnish females found that daily supplementation of 10 μg vitamin D_2 during the winter months for two years was not able to increase serum 25(OH)D concentrations (34, 33 and 30 nmol/l at baseline, 12 months and 24 months respectively) [78]. Even after the dose was increased to 20 μg/day for the third winter, there was only a modest increase in 25(OH)D concentrations to 41 nmol/l. This small increase in circulating 25(OH)D may have been due to the administration of vitamin D_2 which has been shown to have a lower bioavailability compared with vitamin D_3 and consequently increase 25(OH)D concentrations to a lesser extent [79,80]. In French 13–16 year old males, Guillemant et al. found that 2500 μg vitamin D_3 every 2 months for 6 months during the winter (equivalent to ~40 μg/day), maintained post-summer 25(OH)D concentrations (54 nmol/l in September and 55 nmol/l in March) [81]. Although this did not improve vitamin D status, it did prevent the seasonal decline in 25(OH)D over the winter-time as seen in the placebo group (20 nmol/l at the end of winter). However, in a multi-ethnic group of female adolescents in the UK (12–14 years) who were vitamin D inadequate at baseline (25(OH)D < 37.5 nmol/l), four doses of 3750 μg vitamin D_2 over 1 year (again equivalent to ~40 μg/day), significantly improved 25(OH)D concentrations from 18 nmol/l at baseline to 56 nmol/l post-intervention (vs. 16 nmol/l in the placebo group) [82]. Conversely, while intakes of 10 and 20 μg/day vitamin D_3 did improve the vitamin D status of severely deficient females of Pakistani origin residing in Denmark, 25(OH)D concentrations remained below 50 nmol/l, demonstrating that higher intakes may be required [83]. Middle Eastern populations are at a higher risk of vitamin D deficiency and intakes equivalent to approximately 5, 20 and 40 μg/day have not ensured vitamin D adequacy in the majority of the population, although intakes of 50 μg/day did achieve concentrations of >50 nmol/l in 95% of Lebanese adolescents, as well as black African American adolescents, with inadequate baseline concentrations [84,85].

Overall it can be seen that vitamin D intakes of between 20 and 50 μg/day may be required to achieve adequate 25(OH)D concentrations of ≥50 nmol/l in adolescents during times of minimal sun exposure, although this is dependent on the baseline 25(OH)D concentration of the population. The assumption that a vitamin D intake needed to reach a specified 25(OH)D concentration is the same across all population and ethnic groups, whose risk of vitamin D deficiency differs, may be incorrect.

6.1. Vitamin D supplementation and measures of bone health

As previously discussed, a recent systematic review concluded that vitamin D supplementation may lead to improvements in bone density in children and adolescents with low (<35 nmol/l) circulating 25(OH)D concentrations [39]. While the evidence is conflicting, some randomized controlled trials have reported moderate positive effects of vitamin D supplementation on bone mineral accrual in female adolescents with baseline 25(OH)D concentrations <50 nmol/l, however this seems to be further complicated by maturational status, with effects predominantly noted in pre- or early-pubertal females. Ward et al. found no effect of vitamin D_2 supplementation equivalent to ~41 μg/day for 1 year on radial or lumbar spine bone measures in 12–14 year old post-menarcheal females, despite serum 25(OH)D concentrations increasing from 18 nmol/l at baseline to 56 nmol/l post-intervention [82]. In Lebanese females (10–17 years) with low baseline serum 25(OH)D concentrations of 35 nmol/l, vitamin D_3 supplementation equivalent to 5 and 50 μg/day for 1 year increased lumbar spine and hip BMD in a dose-dependent manner in pre-menarcheal females, while no significant changes were observed in post-menarcheal females [86]. Furthermore, this study also reported no consistent positive effect of vitamin D_3 supplementation on BMD in the male participants. Likewise, 7500 μg vitamin D_2 administered quarterly (~82 μg/day) to Indian females with a baseline serum 25(OH)D concentration of 25 nmol/l, significantly improved size-adjusted total body and lumbar spine bone mineral content in those who were ≤2 years since the onset of menarche only [87]. A school-milk intervention trial in China randomized vitamin D deficient (25(OH)D <25 nmol/l) 10–12 year old females to three groups who consumed calcium and vitamin D fortified milk (660 mg calcium and 4 μg vitamin D/day), calcium only fortified milk (650 mg calcium and 0.6 μg vitamin D/day) or their habitual diet (<450 mg calcium and 0.6 μg vitamin D/day) for 2 years [88]. Those in the calcium and vitamin D fortified milk group demonstrated greater changes in size-adjusted total body BMD than those in the calcium fortified milk and control groups. Furthermore, serum 25(OH)D increased from 21 nmol/l to 48 nmol/l in this group, whilst remaining below 20 nmol/l in the groups receiving no additional vitamin D. Two similar randomized controlled trials in adolescent females (9–15 years) that administered 800 mg calcium alongside 10 μg vitamin D daily for 6–12 months, reported significant gains in trabecular BMD of the radius and tibia compared to the placebo groups [89,90]. However neither study measured circulating 25(OH)D concentrations at either baseline or following the intervention, and so it is not known if these adolescents were vitamin D deficient or replete at the onset of the study and it therefore cannot be determined if the positive skeletal gains were due to greater calcium intakes alone, enhanced calcium absorption due to increased vitamin D, or a direct effect of the vitamin D. Promoting calcium absorption may be one mechanism by which vitamin D exerts positive skeletal effects, although the aforementioned studies that did report skeletal gains did not measure calcium absorption. The few intervention trials investigating the effect of vitamin D supplementation on calcium absorption in children and adolescents with serum 25(OH)D concentrations ranging from low to adequate (28–70 nmol/l) have found no effect of vitamin D (range 10–100 μg/day) on calcium absorption [35,36,91]. Finally, vitamin D supplementation between 5 and 100 μg/day has been shown to inhibit winter-time increases in PTH in adolescents [33,36,38,77]. However, PTH concentration as a determinant of vitamin D status in adolescents may be hindered by uncertainties surrounding the beneficial or detrimental effects of elevated PTH concentrations on bone accretion during puberty as previously discussed (see Section 3).

7. Conclusion

Recent studies have demonstrated a high prevalence of low vitamin D status in otherwise healthy adolescents, which raises concerns about long-term health consequences that may evolve from this insufficiency, especially since adolescence is a critical time for bone accretion. Circulating 25(OH)D concentrations along with a functional outcome measure (e.g. bone density) should be used to define what constitutes an adequate vitamin D status. Further studies specifically targeting adolescents, are needed to determine the optimal 25(OH)D concentration for maximal bone acquisition during this critical period of growth, also taking into

consideration the effects on PTH concentrations and calcium absorption. Vitamin D intervention trials with bone density outcomes are limited to white female adolescents and so more data is required in male and ethnic minority adolescents. Furthermore, dose-response vitamin D intervention studies are best suited to establish the vitamin D intake that will be required to achieve this desirable level of adequacy in adolescents. Given that adolescents are a population group with the greatest risk of vitamin D deficiency these research areas should be given a high priority.

Conflict of interest

Authors have no conflict of interest to declare.

Authors' contributions

TJS: drafted the manuscript; TJS, SAL-N, and KHH: had primary responsibility for the final content. All authors read and approved the final manuscript.

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References

[1] J.M. Pettifor, Nutritional rickets: deficiency of vitamin D, calcium, or both? Am. J. Clin. Nutr. 80 (2004) 1725S–1729S.
[2] A.M. Parfitt, J.C. Gallagher, R.P. Heaney, C.C. Johnston, R. Neer, G.D. Whedon, Vitamin D and bone health in the elderly, Am. J. Clin. Nutr. 36 (1982) 1014–1031.
[3] T.A. Outila, M.U. Kärkkäinen, C.J. Lamberg-Allardt, Vitamin D status affects serum parathyroid hormone concentrations during winter in female adolescents: associations with forearm bone mineral density, Am. J. Clin. Nutr. 74 (2001) 206–210.
[4] M.K. Lehtonen-Veromaa, T.T. Möttönen, I.O. Nuotio, K.M. Irjala, A.E. Leino, J.S. Viikari, Vitamin D and attainment of peak bone mass among peripubertal Finnish girls: a 3-y prospective study, Am. J. Clin. Nutr. 76 (2002) 1446–1453.
[5] D.A. Wahl, C. Cooper, P.R. Ebeling, M. Eggersdorfer, J. Hilger, K. Hoffmann, R. Josse, J.A. Kanis, A. Mithal, D.D. Pierroz, J. Stenmark, E. Stöcklin, B. Dawson-Hughes, A global representation of vitamin D status in healthy populations, Arch. Osteoporos. 7 (2012) 155–172, doi:http://dx.doi.org/10.1007/s11657-012-0093-0.
[6] M.F. Holick, Vitamin D deficiency, New Engl. J. Med. 357 (2007) 266–281, doi:http://dx.doi.org/10.1056/NEJMra070553.
[7] M.F. Holick, T.C. Chen, Vitamin D deficiency: a worldwide problem with health consequences, Am. J. Clin. Nutr. 87 (2008) 1080S–1086S.
[8] M.S. Calvo, S.J. Whiting, C.N. Barton, Vitamin D intake: a global perspective of current status, J. Nutr. 135 (2005) 310–316.
[9] I. Elmadfa, A.L. Meyer, V. Nowak, V. Hasenegger, P. Putz, R. Verstraeten, A.M. Remaut-DeWinter, P. Kolsteren, J. Dostálová, P. Dlouhý, E. Trolle, S. Fagt, A. Biltoft-Jensen, J. Mathiessen, M. Velsing Groth, European nutrition and health report 2009, Ann. Nutr. Metab. 55 (2009) 1–40, doi:http://dx.doi.org/10.1159/000244607.
[10] A. Spiro, J.L. Buttriss, Vitamin D: An overview of vitamin D status and intake in Europe, Nutr. Bull. 39 (2014) 322–350, doi:http://dx.doi.org/10.1111/nbu12108.
[11] T. Piirainen, K. Laitinen, E. Isolauri, Impact of national fortification of fluid milks and margarines with vitamin D on dietary intake and serum 25-hydroxyvitamin D concentration in 4-year-old children, Eur. J. Clin. Nutr. 61 (2007) 123–128, doi:http://dx.doi.org/10.1038/sj.ejcn.160250.
[12] S. Soininen, A.-M. Eloranta, V. Lindi, T. Venäläinen, N. Zaproudina, A. Mahonen, T.A. Lakka, Determinants of serum 25-hydroxyvitamin d concentration in finnish children: the physical activity and nutrition in children (PANIC) study, Br. J. Nutr. 115 (2016) 1080–1091, doi:http://dx.doi.org/10.1017/S0007114515005292.
[13] M. Lehtonen-Veromaa, T. Möttönen, A. Leino, O.J. Heinonen, E. Rautava, J. Viikari, Prospective study on food fortification with vitamin D among adolescent females in Finland: minor effects, Br. J. Nutr. 100 (2008) 418–423, doi:http://dx.doi.org/10.1017/S0007114508894469.
[14] L.V. Van Horn, R. Bausermann, S. Affenito, D. Thompson, R. Striegel-Moore, D. Franko, A. Albertson, Ethnic differences in food sources of vitamin D in adolescent American girls: the National Heart, Lung, and Blood Institute Growth and Health Study, Nutr. Res. 31 (2011) 579–585, doi:http://dx.doi.org/10.1016/j.nutres.2011.07.003.
[15] V.L. Fulgoni, D.R. Keast, R.L. Bailey, J. Dwyer, Foods, fortificants, and supplements: where do Americans get their nutrients? J. Nutr. 141 (2011) 1847–1854, doi:http://dx.doi.org/10.3945/jn.111.142257.
[16] R.L. Bailey, K.W. Dodd, J.A. Goldman, J.J. Gahche, J.T. Dwyer, A.J. Moshfegh, C.T. Sempos, M.F. Picciano, Estimation of total usual calcium and vitamin D intakes in the United States, J. Nutr. 140 (2010) 817–822, doi:http://dx.doi.org/10.3945/jn.109.118539.
[17] A. Prentice, G.R. Goldberg, I. Schoenmakers, Vitamin D across the lifecycle: physiology and biomarkers, Am. J. Clin. Nutr. 88 (2008) 500S–506S.
[18] Institute of Medicine, Dietary Reference Intakes for Calcium and Vitamin D, National Academies Press, Washington (DC), 2011.
[19] J.M. Pettifor, P. Ross, J. Wang, G. Moodley, J. Couper-Smith, Rickets in children of rural origin in South Africa: is low dietary calcium a factor, J. Pediatr. 92 (1978) 320–324.
[20] F. Okonofua, D.S. Gill, Z.O. Alabi, M. Thomas, J.L. Bell, P. Dandona, Rickets in Nigerian children: a consequence of calcium malnutrition, Metabolism 40 (1991) 209–213.
[21] T.D. Thacher, P.R. Fischer, J.M. Pettifor, J.O. Lawson, C.O. Isichei, J.C. Reading, G. M. Chan, A comparison of calcium Vitamin D, or both for nutritional rickets in nigerian children, New Engl. J. Med. 341 (1999) 563–568.
[22] European food safety authority panel on dietetic products, nutrition and allergies, dietary reference values for vitamin D, EFSA J. 14 (4547) (2016), doi:http://dx.doi.org/10.2903/j.efsa.2016.4547.
[23] C.L. Wagner, F.R. Greer, the Section on Breastfeeding and Committee on Nutrition, Prevention of rickets and vitamin D deficiency in infants, children, and adolescents, Pediatrics 122 (2008) 1142–1152, doi:http://dx.doi.org/10.1542/peds. 2008-1862.
[24] C. Braegger, C. Campoy, V. Colomb, T. Decsi, M. Domellof, M. Fewtrell, I. Hojsak, W. Mihatsch, C. Mølgaard, R. Shamir, D. Turck, J. van Goudoever, on behalf of the ESPGHAN Committee on Nutrition, Vitamin D in the healthy european paediatric population, J. Pediatr. Gastroenterol. Nutr. 56 (2013) 692–701, doi:http://dx.doi.org/10.1097/MPG.0b013e31828f3c05.
[25] M.F. Holick, N.C. Binkley, H.A. Bischoff-Ferrari, C.M. Gordon, D.A. Hanley, R.P. Heaney, M.H. Murad, C.M. Weaver, Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline, J. Clin. Endocrinol. Metab. 96 (2011) 1911–1930, doi:http://dx.doi.org/10.1210/jc.2011-0385.
[26] Society for Adolescent Health and Medicine, Recommended vitamin D intake and management of low Vitamin D status in adolescents: a position statement of the society for adolescent health and medicine, J. Adolesc. Health 52 (2013) 801–803, doi:http://dx.doi.org/10.1016/j.jadohealth.2013.03.022.
[27] P. Lips, Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications, Endocr. Rev. 22 (2001) 477–501.
[28] S.A. Abrams, I.J. Griffin, K.M. Hawthorne, S.K. Gunn, C.M. Gundberg, T.O. Carpenter, Relationships among vitamin D levels, parathyroid hormone, and calcium absorption in young adolescents, J. Clin. Endocrinol. Metab. 90 (10) (2005) 5576–5581.
[29] F.A. Tylavsky, K.M. Ryder, R. Li, V. Park, C. Womack, J. Norwood, L.D. Carbone, S. Cheng, Preliminary findings: 25(OH)D levels and PTH are indicators of rapid bone accrual in pubertal children, J. Am. Coll. Nutr. 26 (2007) 462–470, doi:http://dx.doi.org/10.1080/07315724.2007.10719637.
[30] L. Harkness, B. Cromer, Low levels of 25-hydroxy vitamin D are associated with elevated parathyroid hormone in healthy adolescent females, Osteoporos. Int. 16 (2005) 109–113, doi:http://dx.doi.org/10.1007/s00198-004-1656-8.
[31] K.M. Hill, G.P. McCabe, L.D. McCabe, C.M. Gordon, S.A. Abrams, C.M. Weaver, An inflection point of serum 25-hydroxyvitamin d for maximal suppression of parathyroid hormone is not evident from multi-Site pooled data in children and adolescents, J. Nutr. 140 (2010) 1983–1988, doi:http://dx.doi.org/10.3945/jn.110.124966.
[32] T.R. Hill, A.A. Cotter, S. Mitchell, C.A. Boreham, W. Dubitzky, L. Murray, J.J. Strain, A. Flynn, P.J. Robson, J.M.W. Wallace, M. Kiely, K.D. Cashman, Vitamin D status and parathyroid hormone relationship in adolescents and its association with bone health parameters: analysis of the Northern Ireland Young Heart's Project, Osteoporos. Int. 21 (2010) 695–700, doi:http://dx.doi.org/10.1007/s00198-009-0959-1.
[33] K. Rajakumar, C.G. Moore, J. Yabes, F. Olabopo, M.A. Haralam, D. Comer, J. Bogusz, A. Nucci, S. Sereika, J. Dunbar-Jacob, M.F. Holick, S.L. Greenspan, Effect of vitamin D3 supplementation in black and in white children: a randomized, placebo-controlled trial, J. Clin. Endocrinol. Metab. 100 (2015) 3183–3192, doi:http://dx.doi.org/10.1210/jc.2015-1643.
[34] S.A. Abrams, P.D. Hicks, K.M. Hawthorne, Higher serum 25-hydroxyvitamin d levels in school-Age children are inconsistently associated with increased calcium absorption, J. Clin. Endocrinol. Metab. 94 (2009) 2421–2427, doi:http://dx.doi.org/10.1210/jc.2008-2587.
[35] C.Y. Park, K.M. Hill, A.E. Elble, B.R. Martin, L.A. DiMeglio, M. Peacock, G.P. McCabe, C.M. Weaver, Daily supplementation with 25 μg cholecalciferol does not increase calcium absorption or skeletal retention in adolescent girls with low serum 25-hydroxyvitamin d, J. Nutr. 140 (2010) 2139–2144, doi:http://dx.doi.org/10.3945/jn.110.124891.
[36] R.D. Lewis, E.M. Laing, K.M.H. Gallant, D.B. Hall, G.P. McCabe, D.B. Hausman, B. R. Martin, S.J. Warden, M. Peacock, C.M. Weaver, A randomized trial of vitamin D3 supplementation in children: dose-response effects on vitamin D

metabolites and calcium absorption, J. Clin. Endocrinol. Metab. 98 (2013) 4816–4825, doi:http://dx.doi.org/10.1210/jc.2013-2728.
[37] H.A. Bischoff-Ferrari, E. Giovannucci, W.C. Willett, T. Dietrich, B. Dawson-Hughes, Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes, Am. J. Clin. Nutr. 84 (2006) 18–28.
[38] H.T. Viljakainen, A.-M. Natri, M. Kärkkäinen, M.M. Huttunen, A. Palssa, J. Jakobsen, K.D. Cashman, C. Mølgaard, C. Lamberg-Allardt, A positive dose-response effect of vitamin D supplementation on site-specific bone mineral augmentation in adolescent girls: a double-blinded randomized placebo-controlled 1-year intervention, J. Bone Miner. Res. 21 (2006) 836–844, doi:http://dx.doi.org/10.1359/jbmr.060302.
[39] T.M. Winzenberg, S. Powell, K.A. Shaw, G. Jones, Vitamin D supplementation for improving bone mineral density in children, Cochrane Database Syst. Rev. 10 (2010), doi:http://dx.doi.org/10.1002/14651858.CD006944.pub2.
[40] R. Bouillon, N.M.V. Schoor, E. Gielen, S. Boonen, C. Mathieu, D. Vanderschueren, P. Lips, Optimal Vitamin D status: a critical analysis on the basis of evidence-based medicine, J. Clin. Endocrinol. Metab. 98 (2013) E1283–E1304, doi:http://dx.doi.org/10.1210/jc.2013-1195.
[41] D.D. Bikle, E. Gee, B. Halloran, M.A. Kowalski, E. Ryzen, J.G. Haddad, Assessment of the free fraction of 25-hydroxyvitamin D in serum and its regulation by albumin and the vitamin D-binding protein, J. Clin. Endocrinol. Metab. 63 (1986) 954–959.
[42] C.M. Mendel, The free hormone hypothesis: a physiologically based mathematical model, Endocr. Rev. 10 (1989) 232–274.
[43] R.F. Chun, B.E. Peercy, E.S. Orwoll, C.M. Nielson, J.S. Adams, M. Hewison, Vitamin D and DBP: the free hormone hypothesis revisited, J. Steroid Biochem. Mol. Biol. A 144 (2014) 132–137, doi:http://dx.doi.org/10.1016/j.jsbmb.2013.09.012.
[44] C.E. Powe, M.K. Evans, J. Wenger, A.B. Zonderman, A.H. Berg, M. Nalls, H. Tamez, D. Zhang, I. Bhan, S.A. Karumanchi, N.R. Powe, R. Thadhani, Vitamin D–binding protein and vitamin D status of black americans and white americans, New Engl. J. Med. 369 (2013) 1991–2000, doi:http://dx.doi.org/10.1056/NEJMoa1306357.
[45] J. Aloia, M. Mikhail, R. Dhaliwal, A. Shieh, G. Usera, A. Stolberg, L. Ragolia, S. Islam, Free 25(OH)D and the vitamin D paradox in African Americans, J. Clin. Endocrinol. Metab. 100 (2015) 3356–3363, doi:http://dx.doi.org/10.1210/JC.2015-2066.
[46] C.E. Powe, C. Ricciardi, A.H. Berg, D. Erdenesanaa, G. Collerone, E. Ankers, J. Wenger, S.A. Karumanchi, R. Thadhani, I. Bhan, Vitamin D-binding protein modifies the vitamin D-bone mineral density relationship, J. Bone Miner. Res. 26 (2011) 1609–1616, doi:http://dx.doi.org/10.1002/jbmr.387.
[47] J.B. Schwartz, J. Lai, B. Lizaola, L. Kane, S. Markova, P. Weyland, N.A. Terrault, N. Stotland, D. Bikle, A comparison of measured and calculated free 25(OH) vitamin D levels in clinical populations, J. Clin. Endocrinol. Metab. 99 (2014) 1631–1637, doi:http://dx.doi.org/10.1210/jc.2013-3874.
[48] M.I. Kamboh, R.E. Ferrell, Ethnic variation in vitamin D-binding protein (GC): a review of isoelectric focusing studies in human populations, Hum. Genet. 72 (1986) 281–293.
[49] J.A. Cauley, L. Lui, K.E. Ensrud, J.M. Zmuda, K.L. Stone, M.C. Hochberg, S.R. Cummings, Bone mineral density and the risk of incident nonspinal fractures in black and white women, JAMA 293 (2005) 2102–2108.
[50] E. Barrett-Connor, E.S. Siris, L.E. Wehren, P.D. Miller, T.A. Abbott, M.L. Berger, A. C. Santora, L.M. Sherwood, Osteoporosis and fracture risk in women of different ethnic groups, J. Bone Miner. Res. 20 (2005) 185–194, doi:http://dx.doi.org/10.1359/JBMR.041007.
[51] M. Pekkinen, E. Saarnio, H.T. Viljakainen, E. Kokkonen, J. Jakobsen, K. Cashman, O. Mäkitie, C. Lamberg-Allardt, Vitamin D binding protein genotype is associated with serum 25-hydroxyvitamin D and PTH concentrations, as well as bone health in children and adolescents in Finland, PLoS One 9 (2014) e87292, doi:http://dx.doi.org/10.1371/journal.pone.0087292.
[52] M. González-Gross, J. Valtueña, C. Breidenassel, L.A. Moreno, M. Ferrari, M. Kersting, S. De Henauw, F. Gottrand, E. Azzini, K. Widhalm, A. Kafatos, Y. Manios, P. Stehle, on behalf of the HELENA Study Group, Vitamin D status among adolescents in Europe: the healthy lifestyle in Europe by nutrition in adolescence study, Br. J. Nutr. 107 (2012) 755–764, doi:http://dx.doi.org/10.1017/S0007114511003527.
[53] M. Absoud, C. Cummins, M.J. Lim, E. Wassmer, N. Shaw, Prevalence and predictors of Vitamin D insufficiency in children: a great britain population based study, PLoS One 6 (2011) e22179, doi:http://dx.doi.org/10.1371/journal.pone.0022179.
[54] National Diet and Nutrition Survey: results from years 1, 2, 3 and 4 (combined) of the Rolling Programme (2008/2009-2011/2012), Public Health England, London. https://www.gov.uk/government/statistics/national-diet-and-nutrition-survey-results-from-years-1-to-4-combined-of-the-rolling-programme-for-2008-and-2009-to-2011-and-2012 (Accessed 11 April 2016).
[55] T.R. Hill, A.A. Cotter, S. Mitchell, C.A. Boreham, W. Dubitzky, L. Murray, J.J. Strain, A. Flynn, P.J. Robson, J.M.W. Wallace, M. Kiely, K.D. Cashman, Vitamin D status and its determinants in adolescents from the Northern Ireland Young Hearts 2000 cohort, Br. J. Nutr. 99 (2008) 1061–1067, doi:http://dx.doi.org/10.1017/S0007114507842826.
[56] J. Öberg, R. Jorde, B. Almås, N. Emaus, G. Grimnes, Vitamin D deficiency and lifestyle risk factors in a Norwegian adolescent population, Scand. J. Public Health 42 (2014) 593–602, doi:http://dx.doi.org/10.1177/1403494814541593.
[57] L.E. Au, C.D. Economos, E. Goodman, A. Must, V.R. Chomitz, J.M. Sacheck, Vitamin D intake and serum vitamin D in ethnically diverse urban schoolchildren, Public Health Nutr. 15 (2012) 2047–2053, doi:http://dx.doi.org/10.1017/S1368980012003217.
[58] V. Ganji, X. Zhang, V. Tangpricha, Serum 25-hydroxyvitamin D concentrations and prevalence estimates of hypovitaminosis D in the U.S. population based on assay-adjusted data, J. Nutr. 142 (2012) 498–507, doi:http://dx.doi.org/10.3945/jn.111.151977.
[59] S.J. Whiting, K.A. Langlois, H. Vatanparast, L.S. Greene-Finestone, The vitamin D status of Canadians relative to the 2011 dietary reference intakes: an examination in children and adults with and without supplement use, Am. J. Clin. Nutr. 94 (2011) 128–135, doi:http://dx.doi.org/10.3945/ajcn.111.013268.
[60] L.H. Foo, Q. Zhang, K. Zhu, G. Ma, A. Trube, H. Greenfield, D.R. Fraser, Relationship between vitamin D status, body composition and physical exercise of adolescent girls in Beijing, Osteoporos. Int. 20 (2009) 417–425, doi:http://dx.doi.org/10.1007/s00198-008-0667-2.
[61] S.H. Kim, M.K. Oh, R. Namgung, M.J. Park, Prevalence of 25-hydroxyvitamin D deficiency in Korean adolescents: association with age, season and parental vitamin D status, Public Health Nutr. 17 (2014) 122–130, doi:http://dx.doi.org/10.1017/S1368980012004703.
[62] S. Puri, R.K. Marwaha, N. Agarwal, N. Tandon, R. Agarwal, K. Grewal, D.H.K. Reddy, S. Singh, Vitamin D status of apparently healthy schoolgirls from two different socioeconomic strata in Delhi: relation to nutrition and lifestyle, Br. J. Nutr. 99 (2008) 876–882, doi:http://dx.doi.org/10.1017/S0007114507831758.
[63] B.R. Santos, L.P.G. Mascarenhas, F. Satler, M.C.S. Boguszewski, P.M. Spritzer, Vitamin D deficiency in girls from South Brazil: a cross-sectional study on prevalence and association with vitamin D receptor gene variants, BMC Pediatr. 12 (2012), doi:http://dx.doi.org/10.1186/1471-2431-12-62.
[64] S.J. Muhairi, A.E. Mehairi, A.A. Khouri, M.M. Naqbi, F.A. Maskari, J.A. Kaabi, A.S. A. Dhaheri, N. Nagelkerke, S.M. Shah, Vitamin D deficiency among healthy adolescents in Al Ain, United Arab Emirates, BMC Public Health 13 (2013), doi:http://dx.doi.org/10.1186/1471-2458-13-33.
[65] A.M. Siddiqui, H.Z. Kamfar, Prevalence of vitamin D deficiency rickets in adolescent school girls in Western region, Saudi Arabia, Saudi Med. J. 28 (2007) 441–444.
[66] K.D. Cashman, K.G. Dowling, Z. Škrabáková, M. Gonzalez-Gross, J. Valtueña, S. De Henauw, L. Moreno, C.T. Damsgaard, K.F. Michaelsen, C. Mølgaard, R. Jorde, G. Grimnes, G. Moschonis, C. Mavrogianni, Y. Manios, M. Thamm, G.B. Mensink, M. Rabenberg, M.A. Busch, L. Cox, S. Meadows, G. Goldberg, A. Prentice, J.M. Dekker, G. Nijpels, S. Pilz, K.M. Swart, N.M. van Schoor, P. Lips, G. Eiriksdottir, V. Gudnason, M.F. Cotch, S. Koskinen, C. Lamberg-Allardt, R.A. Durazo-Arvizu, C.T. Sempos, M. Kiely, Vitamin D deficiency in europe: pandemic? Am. J. Clin. Nutr. 103 (2016) 1033–1044, doi:http://dx.doi.org/10.3945/ajcn.115.120873.
[67] G. El-Hajj Fuleihan, M. Nabulsi, M. Choucair, M. Salamoun, C.H. Shahine, A. Kizirian, R. Tannous, Hypovitaminosis D in healthy schoolchildren, Pediatrics 107 (2001) e53.
[68] F. Ginty, C. Cavadini, P.A. Michaud, M. Baumgartner, G.D. Mishra, D.V. Barclay, Effects of usual nutrient intake and vitamin D status on markers of bone turnover in Swiss adolescents, Eur. J. Clin. Nutr. 58 (2004) 1257–1265, doi:http://dx.doi.org/10.1038/sj.ejcn.1601959.
[69] L. Aksnes, D. Aarskog, Plasma concentrations of vitamin D metabolites in puberty: effect of sexual maturation and implications for growth, J. Clin. Endocrinol. Metab. 55 (1982) 94–101.
[70] Scientific Advisory Committee on Nutrition, Vitamin D and Health, (2016) . (Accessed 21 July 2016) https://www.gov.uk/government/publications/sacn-vitamin-d-and-health-report.
[71] Nordic Council of Ministers, Nordic Nutrition Recommendations 2012. Integrating Nutrition and Physical Activity, 5th ed., Norden, Copenhagen, Denmark, 2014.
[72] German Nutrition Society, New reference values for Vitamin D, Ann. Nutr. Metab. 60 (2012) 241–246, doi:http://dx.doi.org/10.1159/000337547.
[73] Health Council of the Netherlands, Evaluation of the Dietary Reference Values for Vitamin D, Health Council of the Netherlands, The Hague, 2012 (publication no. 2012/15E).
[74] C.A. Nowson, J.J. McGrath, P.R. Ebeling, A. Haikerwal, R.M. Daly, A.M. Sanders, M.J. Seibel, R.S. Mason, Working group of the australian and new zealand bone and mineral society, endocrine society of australia and osteoporosis australia, vitamin D and health in adults in Australia and New Zealand: a position statement, Med. J. Aust. 196 (2012) 686–687, doi:http://dx.doi.org/10.5694/mja11.10301.
[75] World Health Organization and Food and Agriculture Organization of the United Nations, Vitamin and Mineral Requirements in Human Nutrition. Report of a Joint WHO/FAO Expert Consultation, World Health Organization, Geneva, 2004.
[76] K.D. Cashman, A.P. FitzGerald, H.T. Viljakainen, J. Jakobsen, K.F. Michaelsen, C. Lamberg-Allardt, C. Mølgaard, Estimation of the dietary requirement for vitamin D in healthy adolescent white girls, Am. J. Clin. Nutr. 93 (2011) 549–555, doi:http://dx.doi.org/10.3945/ajcn.110.006577.
[77] T.J. Smith, L. Tripkovic, C.T. Damsgaard, C. Mølgaard, C. Ritz, S.L. Wilson-Barnes, K.G. Dowling, Á. Hennessy, K.D. Cashman, M. Kiely, S.A. Lanham-New, K.H. Hart, Estimation of the dietary requirement for vitamin D in adolescents aged 14–18 y: a dose-response, double-blind, randomized placebo-controlled trial, Am. J. Clin. Nutr. 104 (2016) 1301–1309, doi:http://dx.doi.org/10.3945/ajcn.116.138065.
[78] M. Lehtonen-Veromaa, T. Möttönen, I. Nuotio, K. Irjala, J. Viikari, The effect of conventional vitamin D2 supplementation on serum 25(OH)D concentration is weak among peripubertal Finnish girls: a 3-y prospective study, Eur. J. Clin. Nutr. 56 (2002) 431–437, doi:http://dx.doi.org/10.1038/sj/ejcn/1601330.

[79] R.P. Heaney, R.R. Recker, J. Grote, R.L. Horst, L.A.G. Armas, Vitamin D3 is more potent than vitamin D2 in humans, J. Clin. Endocrinol. Metab. 96 (2011) E447–E452, doi:http://dx.doi.org/10.1210/jc.2010-2230.
[80] L. Tripkovic, H. Lambert, K. Hart, C.P. Smith, G. Bucca, S. Penson, G. Chope, E. Hyppönen, J. Berry, R. Vieth, S. Lanham-New, Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis, Am. J. Clin. Nutr. 95 (2012) 1357–1364, doi:http://dx.doi.org/10.3945/ajcn.111.031070.
[81] J. Guillemant, H.-T. Le, A. Maria, A. Allemandou, G. Pérès, S. Guillemant, Wintertime vitamin D deficiency in male adolescents: effect on parathyroid function and response to vitamin D3 supplements, Osteoporos. Int. 12 (2001) 875–879, doi:http://dx.doi.org/10.1007/s001980170040.
[82] K.A. Ward, G. Das, S.A. Roberts, J.L. Berry, J.E. Adams, R. Rawer, M.Z. Mughal, A. Randomized, Controlled trial of vitamin D supplementation upon musculoskeletal health in postmenarchal females, J. Clin. Endocrinol. Metab. 95 (2010) 4643–4651, doi:http://dx.doi.org/10.1210/jc.2009-2725.
[83] R. Andersen, C. Mølgaard, L.T. Skovgaard, C. Brot, K.D. Cashman, J. Jakobsen, C. Lamberg-Allardt, L. Ovesen, Effect of vitamin D supplementation on bone and vitamin D status among Pakistani immigrants in Denmark: a randomised double-blinded placebo-controlled intervention study, Br. J. Nutr. 100 (2008) 197–207, doi:http://dx.doi.org/10.1017/S000711450789430X.
[84] L. Al-Shaar, R. Mneimneh, Nabulsi, J. Maalouf, G.E.-H. Fuleihan, Vitamin D3 dose requirement to raise 25-hydroxyvitamin D to desirable levels in adolescents: results from a randomized controlled trial, J. Bone Miner. Res. 29 (2014) 944–951, doi:http://dx.doi.org/10.1002/jbmr.2111.
[85] Y. Dong, I.S. Stallmann-Jorgensen, N.K. Pollock, R.A. Harris, D. Keeton, Y. Huang, K. Li, R. Bassali, D. -h. Guo, J. Thomas, G.L. Pierce, J. White, M.F. Holick, H. Zhu, A 16-week randomized clinical trial of 2000 international units daily vitamin D3 supplementation in black youth: 25-hydroxyvitamin D, adiposity, and arterial stiffness, J. Clin. Endocrinol. Metab. 95 (2010) 4584–4591, doi:http://dx.doi.org/10.1210/jc.2010-0606.
[86] G. El-Hajj Fuleihan, M. Nabulsi, H. Tamim, J. Maalouf, M. Salamoun, H. Khalife, M. Choucair, A. Arabi, R. Vieth, Effect of vitamin D replacement on musculoskeletal parameters in school children: a randomized controlled trial, J. Clin. Endocrinol. Metab. 91 (2006) 405–412, doi:http://dx.doi.org/10.1210/jc.2005-1436.
[87] A.V. Khadilkar, M.G. Sayyad, N.J. Sanwalka, D.R. Bhandari, N. Sadanand, V.V. Khadilkar, M.Z. Mughal, Vitamin D supplementation and bone mass accrual in underprivileged adolescent Indian girls, Asia Pac. J. Clin. Nutr. 19 (2010) 465–472.
[88] X. Du, K. Zhu, A. Trube, Q. Zhang, G. Ma, X. Hu, D.R. Fraser, H. Greenfield, School-milk intervention trial enhances growth and bone mineral accretion in Chinese girls aged 10–12 years in Beijing, Br. J. Nutr. 92 (2004) 159–168, doi:http://dx.doi.org/10.1079/BJN20041118.
[89] L.J. Moyer-Mileur, B. Xie, S.D. Ball, T. Pratt, Bone mass and density response to a 12-month trial of calcium and vitamin D supplement in preadolescent girls, J. Musculoskelet. Neuronal Interact. 3 (2003) 63–70.
[90] D.A. Greene, G.A. Naughton, Calcium and vitamin-D supplementation on bone structural properties in peripubertal female identical twins: a randomised controlled trial, Osteoporos. Int. 22 (2011) 489–498, doi:http://dx.doi.org/10.1007/s00198-010-1317-z.
[91] S.A. Abrams, K.M. Hawthorne, Z. Chen, Supplementation with 1000 IU vitamin D/d leads to parathyroid hormone suppression, but not increased fractional calcium absorption, in 4–8-y-old children: a double-blind randomized controlled trial, Am. J. Clin. Nutr. 97 (2013) 217–223, doi:http://dx.doi.org/10.3945/ajcn.112.046102.