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REVIEW ARTICLE

Vitamin D and skeletal health in infancy and childhood

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Abstract During growth, severe vitamin D deficiency in childhood can result in symptomatic hypocalcaemia and rickets. Despite the suggestion from some studies of a secular increase in the incidence of rickets, this observation may be driven more by changes in population demographics than a true alteration to age, sex and ethnicity-specific incidence rates; indeed, rickets remains uncommon overall and is rarely seen in fair-skinned children. Additionally, the impact of less severe vitamin D deficiency and insufficiency has received much interest in recent years, and in this review, we consider the evidence relating vitamin D status to fracture risk and bone mineral density (BMD) in childhood and adolescence. We conclude that there is insufficient evidence to support the suggestion that low serum 25-hydroxyvitamin D [25(OH)D] increases childhood fracture risk. Overall, the relationship between 25(OH)D and BMD is inconsistent across studies and across skeletal sites within the same study; however, there is evidence to suggest that vitamin D supplementation in children with the lowest levels of 25(OH)D might improve BMD. High-quality randomised trials are now required to confirm this benefit.

Keywords Bone mineral density · Childhood · Epidemiology · Fracture · Osteoporosis · Rickets · Vitamin D

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Introduction

Severe vitamin D deficiency (VDD) can result in rickets, metabolic bone disease and hypocalcaemia during infant and childhood growth. However, in recent years, there has been increasing interest in the contribution of vitamin D to other aspects of bone health, including fracture risk and bone mineral density (BMD). Concurrently, there has been an increase in the screening for biochemical VDD [1, 2] and a suggested re-emergence of both VDD and rickets in many developed countries [3–7]. In older adults, VDD has been associated with increased fracture risk and there is some evidence that vitamin D (in combination with calcium) supplementation can reduce this [8]. However, as demonstrated by the potentially opposing effects of obesity on fracture occurrence in adults and children [9], the inference of paediatric effects from adult physiology should be approached with caution. In this review, we consider the evidence that insufficient levels of vitamin D may impact adversely on the health of the growing skeleton.

The epidemiology of vitamin D deficiency in childhood

The physiology of vitamin D, including endogenous synthesis by photoconversion of 7-dehydrocholesterol to pre-vitamin D, and its role in calcium and phosphate homeostasis is well understood. We therefore refer the reader to a number of recent review articles from which a detailed exposition of this area may be obtained [10–12].

Serum 25-hydroxyvitamin D [25(OH)D] is currently considered the best marker of vitamin D status, and there is increasing evidence that low 25(OH)D status is common in children. Two recent large UK studies have suggested that around a third of children have a serum 25(OH)D <50 nmol/l [13, 14]. Risk factors for low 25(OH)D include skin pigmentation and lifestyle factors associated with reduced skin exposure to sunlight (including extensive skin covering, less outdoor play and greater sunscreen use), winter months, obesity [15], and even within the UK, children residing in Northern England and Scotland have lower 25(OH)D status than children in Southern England [13, 16]. Therefore, the reported prevalence of VDD is dependent on the population studied; thus, 73 % of adolescent girls in a multi-ethnic school in the UK had a 25(OH)D <30 nmol [17].

However, despite the high prevalence of low serum 25(OH)D, how this might equate to clinical outcomes remains unclear. There is no doubt that severe VDD can lead to symptomatic hypocalcaemia and rickets (for review articles detailing the pathophysiology, clinical and radiological features of rickets, see [10–12, 18, 19]). However, although there has been a suggestion that cases of rickets are increasing in many developed countries, including the UK [3], Australia [4], the USA [6, 5] and Denmark [7], overt rickets remains uncommon. Surveys in the UK, Canada and Australia have reported the incidence of symptomatic VDD (radiographic rickets or hypocalcaemic seizures due to VDD) to be between 2.9 and 7.5 per 100,000 children [20–22], but VDD rickets is rare in white Caucasian children and the majority of cases are reported in children of African and Asian ethnicity [3, 4, 20, 21]; a 2001 survey of VDD rickets in children aged less than 5 years in the West Midlands, UK, estimated the incidence in Caucasian children to be 0.4 per 100,000 compared with 38 per 100,000 in Asian children and 95 per 100,000 in children of Black-African or Afro-Caribbean ethnicity [20]. Furthermore, in Southern Denmark, the overall incidence of VDD rickets had increased in 1995–2005 compared with 1985–1994, yet the incidence actually decreased in ethnic Danish children [7]. In this study, the incidence of nutritional rickets in immigrant children under 3 years of age who had been born in Denmark was fifty times higher than in ethnic Danish children [7].

Comparison of the prevalence of VDD across studies, countries and time is limited by the wide variation in the definition of VDD used. Currently, the suggested threshold for a serum 25(OH)D which is felt to constitute adequacy varies from 25 to 75 nmol/l [23–26]; however, 25(OH)D status has been associated with a wide variety of clinical outcomes across most organ systems. Many definitions for vitamin D sufficiency have been based on a threshold for secondary hyperparathyroidism; however, even in adults, there does not appear to be a single threshold below which this occurs [27]. Similarly in children, extrapolation from a particular serum concentration of 25(OH)D to disease outcomes such as metabolic bone disease and secondary hyperparathyroidism cannot be made with any certainty. The inflection point at which parathyroid hormone (PTH) increases has been documented across a wide range of 25(OH)D concentrations (34–75 nmol/l) [28–30], but an inverse relationship rather than a plateauing of PTH above a given 25(OH)D threshold is also observed in children and adolescents [31–34]. Furthermore, many children with low 25(OH)D do not develop rickets [28], and it is likely that an interaction between vitamin D and dietary calcium modifies the association between 25(OH)D and PTH, and subsequent clinical outcomes [35]. This is particularly important in countries and ethnic groups in which low dietary calcium intake is highly prevalent. Nonetheless, whether other clinical outcomes, such as fracture risk and/or low BMD, should be considered in relation to the threshold for adequacy is currently uncertain and will be discussed later in this review.

Vitamin D and childhood fracture risk

Fractures in Caucasian children are common; up to 50 % of boys and 40 % of girls will sustain at least one fracture before the age of 18 years [36, 37]. Overall, fracture rates are higher in boys than girls; this difference is most evident in adolescence when fracture rates increase rapidly in boys, whereas sex-specific rates tend to be similar in infancy [36, 37]. Lower BMD [38–42], overweight and obesity [9], risk-taking behaviour and poorer socioeconomic background are recognised risk factors for fracture. In both boys and girls, the forearm is the most common site of fracture in childhood, followed by other upper limb sites including carpals, humerus and clavicle [36]. Overall lower limb fractures are less common, although in females under 2 years of age, tibia/fibula fractures occur at a higher rate than forearm or humeral fractures [36].

Fracture in children with vitamin D deficiency rickets

Fracture can be the presenting feature of VDD rickets [3, 4, 6, 22, 43–49]. However, it is relatively uncommon. Overall, across various case series, up to 20 % of cases present in this way, compared with up to 80 % of cases presenting with hypocalcaemic seizures and up to 70 % with skeletal deformity (Table 1). However, the mode of presentation varies

Table 1 Mode of presentation in children with rickets in case series published since 2000

Study	Country	Time period of study	Number of children	Age range	Presenting feature, *n* (%)		
					Fracture	Skeletal deformity	Hypocalcaemic seizure
Agarwal 2009 [112]	India	2006–2008	51	10–13 years	3 (5.9)	19 (37.3)	0 (0.0)
Ahmed 2010 [3]	UK	2002–2008	160	2 weeks–14 years	11 (6.9)	64 (40.0)	19 (11.9)
Al-Atawi 2009 [45]	Saudi Arabia	1990–2000	283	6–14 months	4 (1.4)	NR	98 (40.3)
Al-Jurayyan 2002 [46]	Saudi Arabia	1994–1999	42	6–18 years	3 (7.1)	5 (11.9)	NR
Beck-Nielsen 2009 [47]	Denmark	1985–2005	112	0–15 years	5 (4.5)	NR	15 (13.4)
Blok 2000 [44]	New Zealand	1998	18	3–36 months	1 (5.6)	7 (53.8)	3 (16.7)
Chapman 2010 [49]	USA	2000–2007	32	2–24 months	7 (21.9)	NR	NR
Hatun 2005 [113]	Turkey	2001–2003	47	0–3 months	0 (0.0)	0 (0.0)	33 (78.7)
Lazol 2008 [6]	USA	1995–2005	58	2–132 months	9 (15.5)	23 (39.7)	7 (12.1)
Miyako 2005 [48]	Japan	1992–2001	10	2–31 months	2 (20.0)	7 (70.0)	2 (20.0)
Mylott 2004 [43]	USA	1996–2004	51	4–24 months	5 (9.8)	14 (27.4)	5 (9.8)
Narchi 2001 [114]	Saudi Arabia	1996–1997	21	11–15 years	0 (0.0)	2 (9.5)	NR
Pedersen 2003 [51]	Denmark	1990–1999	40	6 months–15 years	5 (12.5)	17 (42.5)	2 (5.0)
Robinson 2006 [4]	Australia	1993–2003	126	0–15 years	5 (4.0)	28 (22.2)	42 (33.3)
Thacher 2013 [5]	USA	1970–2009	17	0–3 years	0 (0.0)	8 (47.1)	2 (11.8)
Tomaschek 2001 [115]	Georgia	1997–1999	5	8–21 months	0 (0.0)	0 (0.0)	2 (40.0)
Ward 2007 [22]	Canada	2002–2004	104	0–7 years	11 (10.6)	44 (42.3)	20 (19.2)
All studies			1,177		71 (6.0)	238 (31.7)[a]	250 (23.1)[a]

NR not reported

[a] Percentage calculated from studies in which mode of presentation was reported

depending upon age, with hypocalcaemic seizures being documented particularly during early infancy [50, 51]. Therefore, owing to the high incidence of fracture in healthy children and that few of these case series describe fracture mechanisms, a true causal role for VDD is likely to be difficult to establish reliably.

Three studies have examined fracture incidence in children with a diagnosis of rickets. El Desouki et al. performed total body scintigraphy in 26 children and adolescents with rickets or osteomalacia. They reported that "multiple stress fractures" were present in eight (31 %) of the participants, and healing was evident 6 months after vitamin D and calcium therapy [52]. However, these "pseudofractures" were not confirmed radiologically and may have represented Looser zones rather than true fractures. Perez-Rossello et al. identified 26 children with radiographic and biochemical evidence of rickets. At telephone interview follow-up 2–3 years after diagnosis and treatment, no child had sustained a fracture [53]. However, owing to the small number of children included and lack of a healthy control group, it is difficult to draw any conclusions on fracture risk following resolution of rickets. Bener et al. assessed demographic and lifestyle factors and medical history in 540 healthy Qatari children less than 5 years of age. VDD rickets was diagnosed in 129 (24 %) children, based on clinical, biochemical and radiographic signs of rickets and normalisation of alkaline phosphatase (ALP) within 6 weeks of vitamin D supplementation. When comparing the 129 children with rickets to the 411 healthy children, a lifetime history of fracture was significantly more common in those with rickets (22.5 %) than the healthy children (13.5 %, $p=0.01$) [54]. The study suggests an increased risk of fracture in children with rickets, but a lack of detail regarding fracture ascertainment and validation and the possibility that some fractures occurred several years before the diagnosis of rickets are limitations to the interpretation of these findings.

There are few reports regarding the sites of fracture in children with rickets, but in case reports, a variety of sites were involved, including clavicle, radius/ulna, lateral rib and femur [55–60]. Only one study has retrospectively evaluated fracture patterns in children with rickets. Chapman et al. studied 40 infants under 2 years of age with rickets, of whom 32 (71 %) had nutritional rickets [49]. Radiographs obtained within a month of diagnosis were reviewed for the presence of fractures, which were found in seven (17.5 %) children, all of whom had VDD rickets. In those with fractures, between one and four fractures were identified and fracture types included lateral and antero-lateral rib fractures, metaphyseal fractures of the humerus, radius and tibia, and transverse fractures of the ulna, tibia, fibula and metatarsus. Fractures were not identified in non-mobile children in this study. Full

skeletal surveys were not undertaken, and therefore, other fractures might have been missed.

Fracture in non-rachictic children

In older adults, there is some evidence that vitamin D supplementation in combination with calcium supplementation can reduce fracture risk [8]. However, there is some evidence that falls risk may also be reduced [61], possibly through an action on muscle function. It is probably not appropriate to extrapolate such findings to paediatric populations, yet there are very few published data relating vitamin D status to fracture risk in healthy children.

We identified two cross-sectional and six case-control studies (Table 2) investigating vitamin D status in children with fractures. James et al. undertook a cross-sectional survey of 25(OH)D status in 213 children presenting with upper limb fractures in Louisiana, USA. 24 and 41 % of the children were considered to be vitamin D deficient (defined as 25(OH)D <50 nmol/l) and insufficient (25(OH)D 50–75 nmol/l), respectively [62]. African-American children were more likely to be vitamin D deficient than white children, but no difference was identified in 25(OH)D status in children who sustained a fracture from a low trauma compared to a high impact mechanism [62]. Similarly, Ryan et al. identified that ten of 17 (59 %) African-American children aged 5–9 years with a radiographically confirmed forearm fracture had a serum 25(OH)D <50 nmol/l [63]. Neither of these studies included a control group, and therefore, it cannot be determined that the distribution of serum 25(OH)D differed from that in the background population.

Ryan et al. subsequently undertook a case-control study comparing African-American children aged 5–9 years who had suffered an acute forearm fracture with controls who had never sustained a fracture [41]. In univariate analysis of 70 cases and 71 controls, neither mean serum 25(OH)D nor the percentage of children with VDD differed between cases and controls (Table 2) [41]. However, although not statistically significant, a greater proportion of children with fracture were assessed in spring or summer and more control children in winter. After adjustment for age, gender, parental education level, season, physical activity level, high BMI, height, dietary calcium intake, mean daily caloric intake and areal BMD measured by dual energy X-ray absorptiometry (DXA), a serum 25(OH)D <50 nmol/l was associated with a 3.5 times higher odds of forearm fracture [41]. Chan et al. studied 17 children under 12 years who had sustained an accidental fracture. When compared with 17 control children who had no history of fracture, there was no significant difference in serum 25(OH)D [64]. Similarly, Farr et al. assessed 25(OH)D status in 115 children aged 8–15 years who had sustained a mild or moderate impact distal radial fracture. In comparison to 100 children with no history of fracture, 25(OH)D status did

Table 2 Case-control studies of serum 25(OH)D status in children with fractures

Study	Age	Inclusion criteria for children with fractures	Number	Serum 25(OH)D, mean (nmol/l)			Serum 25(OH)D <50 nmol/l (%)		
				Cases	Controls	*p*	Cases	Controls	*p*
Ceroni 2012 (Geneva, Switzerland) [66]	10–16 years	Admission for orthopaedic reduction or surgery to first appendicular fracture. Excluded if taking vitamin D supplementation	100 cases (50 UL, 50 LL) 50 controls	UL: 32 LL: 21	33	NS	UL 12 LL 12	6	NS
Chan 1984[a] (Salt Lake City, USA) [64]	2–12 years	Hospitalisation with fracture	17 cases 17 controls	70	77	0.45			
Farr 2014[a] (Olmsted County, MN, USA) [65]	8–15 years	Mild or moderate impact fracture of the distal radius (with or without ulna fracture) within the preceding year	Males 63 cases, 58 controls Females 52 cases, 50 contols	72 68	69 73	0.45 0.25			
Mäyränpää 2012 (Helsinki, Finland) [67]	4–16 years	Two low-energy fractures ≤10 years or three low-energy fractures ≤16 years or one low-energy vertebral fracture	64 cases 69 controls	42	43	0.64	73	69	0.63
Olney 2008[a] (FL, USA) [68]	3–18 years	At least two low-energy fractures	68 cases 57 controls				21	18	NS
Ryan 2012[a] (Washington DC, USA) [41]	5–9 years	African-American with forearm fracture	70 cases 71 controls	55	56	0.59	47	41	0.45

NS non-significant, *UL* upper limb, *LL* lower limb

[a] In these studies, 25(OH)D was originally reported in nanograms per millilitre (ng/ml). It has been converted to nanomoles per litre (nmol/l) using a conversion factor of 1 ng/ml=2.49 nmol/l. These studies used a cut-point for deficiency of <20 ng/ml which is approximately equivalent to <50 nmol/l

not differ [65]. However, in both of these studies, 25(OH)D status was not assessed at the time of fracture but at approximately 16 months after fracture in the study by Chan et al. and within 1 year of fracture in the study of Farr et al. Therefore, vitamin D status at the time of study inclusion might not have reflected that at the time of fracture due to seasonal and dietary variability. Furthermore, it is not stated in either study at what time of year blood sampling took place or if this was similar between cases and controls. Similarly, Ceroni et al. found no significant difference in 25(OH)D in adolescents admitted for surgical management of a first appendicular fracture compared to healthy controls with no history of fracture [66].

Two case-control studies included only children with a history of at least two low-energy trauma fractures. Although low vitamin D status was highly prevalent in both studies, serum 25(OH)D was comparable between fracturing children and healthy controls (Table 2) [67, 68]. Mäyränpää et al. additionally obtained prone thoracolumbar spine radiographs in 64 fracture children, and those who had evidence of a vertebral compression fracture (traumatic $n=11$; asymptomatic $n=8$) did, on average, have a significantly lower mean serum 25(OH)D than those who had not, although 25(OH)D alone provided insufficient discriminative power to reliably identify subjects as belonging to fracture or non-fracture groups [67].

Two studies reported on lifetime fracture history in children according to current vitamin D status. Bener et al. measured 25(OH)D in 458 healthy Qatari children under the age of 15 years. Lifetime fracture history, as determined by parental interview, was significantly higher in children with 25(OH)D <50 nmol/l (18.4 vs 8.4 %, $p=0.006$) [54]. In a study of 890 obese children in Arkansas, USA, 22 % were defined as vitamin D deficient (25(OH)D <40 nmol/l) and had a 1.82 increased risk of a documented fracture history than the vitamin D replete children ($p=0.05$) [69]. Interestingly, when both parentally reported and hospital documented fractures were considered, this excess risk was no longer present. Increased adiposity is a recognised independent risk factor for both childhood fracture [9] and lower 25(OH)D status [15]. Thus, in the study of obese children, differences in BMI and age between vitamin D deficient and replete children should be considered in the interpretation of the documented findings [68].

Fracture healing

Animal studies have suggested that vitamin D supplementation can improve fracture healing, but there is a paucity of human data in this area [70], and we could identify none in children. One case-control study in Poland found no difference in serum 25(OH)D in otherwise healthy adults with and without fracture non-union [71].

Vitamin D and bone mineralisation

Bone mineral density in vitamin D deficiency rickets

It has been suggested that the secondary hyperparathyroidism in early rickets results in demineralisation and generalised osteopenia. Whilst this might be evident on radiographs, it is highly subjective [72], and there is little objective evidence to demonstrate mineralisation defects in children with clinical rickets. Three studies have measured bone mineralisation by DXA in children diagnosed with VDD rickets. Akcam et al. assessed lumbar spine areal BMD (aBMD) in 20 children age 5–13 months with clinical, biochemical and radiographic evidence of VDD rickets before and 1 month after vitamin D treatment [73]. Lumbar spine aBMD did increase significantly in two different treatment regimens; however, as the study was designed to compare these treatment regimens, a control group was not included [73]. Ergur et al. evaluated forearm bone mineral content (BMC) and aBMD in fourteen infants under 1 year of age with VDD rickets diagnosed by clinical evaluation in association with either biochemical or radiographic features and fourteen healthy controls of similar age [74]. No differences in mineralisation were identified. Conversely, a report of 26 children and adolescents with osteomalacia and/or rickets in Saudi Arabia suggested that aBMD Z-scores at the lumbar spine (LS) and FN femur were reduced and that these improved following calcium and vitamin D therapy [52]. It is unclear though whether these differences were statistically significant.

Vitamin D in pregnancy and offspring BMD

The developing fetus is dependent on placental transfer of 25(OH)D from the maternal circulation. Whilst early rickets and neonatal hypocalcaemia do rarely occur as a result of severe maternal VDD [75–77], there is growing evidence to support an important role for maternal 25(OH)D status in pregnancy in determining offspring BMD. To date, the available data are primarily observational in nature [78], although a recent systematic review concluded that there was some evidence to support a positive association between maternal 25(OH)D status and offspring bone mass [79]. There is currently only one intervention study of vitamin D supplementation in pregnancy which included an assessment of offspring bone mineralisation; this was a small non-randomised study of 19 newborn infants of Asian mothers who had taken 1,000 IU vitamin D in a combined calcium and vitamin D supplement daily during the last trimester of pregnancy and 45 babies of Asian women who had not received any form of vitamin D supplementation in pregnancy. Single photon absorptiometry was used to assess BMC of the forearm. No significant differences were identified, but the small participant numbers, technique used to assess BMC and lack of randomisation

mean it is difficult to draw any definite conclusions from this study [80]. Overall, current evidence is insufficient to support any clinical recommendation for vitamin D supplementation in pregnancy but highlights the need for high-quality randomised controlled trials. The UK Maternal Vitamin D Osteoporosis Study (MAVIDOS), which primarily aims to compare neonatal bone mass in infants born to mothers randomised to vitamin D supplementation or placebo during pregnancy, will directly address this gap in the evidence [81].

Infant vitamin D status and BMD

Two cross-sectional studies in infancy found no associations between serum 25(OH)D and whole-body BMC at 3 months of age [82] or LS BMC at 2–5 months [83]. Four intervention studies of vitamin D supplementation in breast-fed infants have reported outcomes related to bone mineralisation. In all but one study [84], serum 25(OH)D was greater in the supplemented infants, but no differences in BMC or BMD were identified at 3 [85], 6 [86] or 12 months [86, 87] of age. In one study, a significantly greater distal radius BMC measured by single-photon absorptiometry was measured in the supplemented infants at 12 weeks of age but not at 26 weeks of age [84].

Vitamin D status and BMD in childhood and adolescence

There were no studies reporting relationships between serum 25(OH)D and bone mineralisation in healthy preschool children after 1 year of age. This is likely due to the limitations of methods for assessing BMD. DXA scans require children to lie still to prevent movement artefact, and whilst babies can be swaddled to minimise movement, the successful acquisition of DXA scans in older infants and toddlers presents a substantial challenge.

A number of cross-sectional studies in older children and adolescents have investigated the associations between 25(OH)D status and aBMD, BMC or bone mineral apparent density (BMAD), a mathematical transformation to estimate volumetric BMD (vBMD) from DXA. The findings of these studies are somewhat inconsistent, both at the same skeletal sites across studies and at different skeletal sites within the same population [33, 66, 67, 88–101] (Table 3). However, there is considerable variation in the age of study participants, geographic location and the confounding factors considered.

Fewer studies have used peripheral quantitative computed tomography (pQCT) to assess true vBMD: Cheng et al. found that 25(OH)D was positively associated with cortical vBMD at the radius in Finish pre-pubertal and early pubertal girls although did not identify any significant associations with the whole body, lumbar spine or total hip aBMD using DXA [90]. Talwar et al. identified positive, but not statistically significant, relationships between 25(OH)D and radial vBMD in a small study of African-American girls [95]. Warden et al. also did not find significant univariate relationships between 25(OH)D and tibial cortical vBMD in either white nor black children in early puberty; however, when race and 25(OH)D were included in a multivariate model, 25(OH)D was a significant predictor of tibial cortical vBMD [100]. Furthermore, the relationship between 25(OH)D and geometric properties of bone differed by ethnicity; negative relationships were observed with total bone area and strength-strain index, a measure of bone strength, in the black children but not the white children, highlighting the potential importance of ethnicity to the relationships between 25(OH)D and bone development.

Several studies examined BMD across groups according to either tertiles [89, 92, 101] or pre-defined cut-points for 25(OH)D [33, 88, 90, 102, 103]. Despite variations in the definition used, five out of the seven studies found that children and adolescents with the lowest levels of serum 25(OH)D had significantly lower BMD at one or more skeletal site, although one research group found this was only evident in girls and not boys [102, 89] and another only in more sexually mature girls [91]. The two studies that reported no significant difference were based on cohorts of ballet dancers [101, 103] and highlight the need for caution in the interpretation of cross-sectional studies relating vitamin D status to clinical outcomes. As vitamin D status is primarily dependent on sunlight exposure, confounding and reverse causality are significant issues which must be considered. For example, outdoor physical activity will both increase 25(OH)D status and have a positive effect on BMD. In one study of 16 male adolescent ballet dancers, there was a non-significantly greater whole body and lumbar spine aBMD Z-score in those with 25(OH)D <50 nmol/l [103]; the low vitamin D group had been training for longer and for more hours a week. Similarly, Constantini et al. found no differences in the whole body, lumbar spine nor femoral neck aBMD across tertiles of 25(OH)D in adolescent females, but a third of participants were ballet dancers, and the proportion of dancers was greatest in the lowest tertiles of 25(OH)D [101]. In both of these studies, it is possible that high levels of indoor physical activity partly confounded the findings. Overall, these studies suggest that the relationship between 25(OH)D and BMD is non-linear, and BMD is predominantly affected in severe VDD; however, only one study, which found no association between 25(OH)D and forearm BMD, also assessed PTH, and this found no association between PTH and BMD [33].

Furthermore, the interpretation of cross-sectional studies is limited by a single measurement of 25(OH)D, which in most countries is subject to seasonal variation. For example, in preschool children in the UK, mean 25(OH)D was approximately 70 % higher in summer compared to winter [16], yet the potential tracking of 25(OH)D throughout the year has not

Table 3 Cross-sectional studies investigating the associations between serum 25(OH)D (as a continuous variable) and areal bone mineral density assessed by DXA in children and adolescents

Study (country of study)	Age	Number and gender	Months in which study conducted	Bone mineral density					Comments
				Whole body	Lumbar spine	Femoral neck	Total hip	Forearm	
Ceroni 2012 [66] (Switzerland)	10–16 years	150	January–December		0				Included 100 adolescents with acute fracture and 50 healthy controls with no history of fracture
Cheng 2003 [90] (Finland)	10–12 years	193 F	December and January	0	0	0			
Lee 2013 [88] (Korea)	5–14 years	100 (45 M, 55 F)	December–March and June–September	+	+				Adjusted for physical activity, calcium intake, gender, pubertal status, fat mass, lean mass
Marwaha 2005 [97] (India)	10–18 years	555	Not stated					0	
Mäyränpää 2012 [67] (Finland)	4–17 years	66 (44 M, 22 F)	January–December	+					Only children with multiple fractures. Adjusted for season of 25(OH)D only
Mouratidou 2013 [92] (Spain)	12–17 years	48 M	January–December	0	0		0	0	Adjusted for height, socioeconomic status, pubertal status, physical activity, age at menarche, season of blood sampling
	12–17 years	53 F		+	0		0	+	
Outila 2001 [33] (Finland)	14–16 years	178 F	February–March					0	Adjusted for BMI, age, height velocity, calcium intake, serum PTH, physical activity, smoking, alcohol intake
Pekkinen 2013 [93] (Finland)	7–19 years	195 (75 M, 120 F)	November–March	+	+		+		Adjusted for age, gender, height, physical activity, body fat percentage (LS and hip only), lean mass (LS only)
Stein 2006 [94] (USA)	4–8 years	168 F	January–December	0	0	0		0	Adjusted for season, ethnicity, age, BMI, calcium intake, physical activity
Talwar 2007 [95] (USA)	12–14 years	21 F	February–April	0	0			0	African-American females only

F female, *M* male, *LS* lumbar spine, *BMI* body mass index, *PTH* parathyroid hormone, *0* = assessed, no association, + = positive association, blank boxes = not assessed

been elucidated. Reproducibility of 25(OH)D status in samples obtained in the same month at 1- to 5-year intervals has been demonstrated in adults [104, 105]. However, stability in the rank of an individual's 25(OH)D measurement within the population distribution at several time points during childhood/adolescence or across seasons is unknown. Varying methods have been used to account for this, including conducting the study only during winter months (Table 3). However, even comparing two Finnish studies of similar sizes and both sampling in winter months, one identified positive relationships between 25(OH)D and BMD [93], whereas the other did not [90]. Alternatively, some authors have adjusted the relationships between 25(OH)D and BMD for season of blood sampling [67, 92, 94]. This, however, assumes the tracking of vitamin D status between seasons, and despite this approach, the findings remain inconsistent with both positive [67, 92] and null [92, 94] relationships reported.

Intervention studies are necessary to address the longitudinal variation in 25(OH)D status, and randomised controlled trials can eliminate potential known and unknown confounding factors. A recent meta-analysis of six randomised controlled trials of vitamin D supplementation for at least 3 months in healthy children and adolescents found no significant gain in the whole body, forearm, hip or lumbar spine aBMD. However, in children with a baseline 25(OH)D <35 nmol/l, beneficial effects of vitamin D supplementation on the whole body and lumbar spine aBMD of borderline significance were identified [106], suggesting the possibility of a benefit of supplemental vitamin D in those with the lowest circulating 25(OH)D concentrations.

Discussion

It is well established that severe VDD can lead to overt rickets, osteomalacia and symptomatic hypocalcaemia. However, these outcomes remain relatively uncommon. In the UK, the overall incidence of rickets at 7.5 per 100,000 [20] is approximately equal to that of childhood leukaemia [107]. However, for Caucasian children, the lifetime risk of childhood leukaemia far exceeds that of rickets. Nonetheless, vitamin D deficiency rickets is a treatable disease and targeting preventative strategies at high risk populations, in whom the incidence rates are up to 200 times that of white children [20] may be appropriate. Indeed, the incidence of symptomatic VDD in children aged less than 5 years more than halved following the introduction of universal free vitamin D supplements for all pregnant women and children under 5 years in Birmingham, where 75 % of the population are from high risk ethnic backgrounds [108].

Several studies have suggested a secular increase in the absolute numbers of children presenting with symptomatic VDD [3, 5, 7, 6, 109, 4], but few of these report actual incidence rates [5, 7]. As such, temporal changes in population size might be contributing to the observed increases. Ethnic diversity is also changing in many developed countries; thus, the proportion of the population who are dark-skinned children and at high risk of rickets has increased in many areas. For example, in England and Wales, the proportion of the population defining themselves as white ethnicity reduced from 94.1 % in 1991 to 91.3 % and 86.0 % in 2001 and 2011, respectively [110]. This is likely to result in an increase in the absolute numbers of cases treated, but it is currently unclear whether there is truly an increase in ethnicity-specific incidence rates. Furthermore, there are no data to support an increasing incidence of rickets in white Caucasian children, and in Denmark, a reduction in the incidence in ethnic Danish children has been observed [7].

It is possible that heightened awareness of vitamin D in both health professionals and the general public, in association with greater reporting in scientific and lay media, are contributing to an increase in biochemical testing of 25(OH)D status [1, 2] and detection of asymptomatic low levels of 25(OH)D. However, the evidence to suggest that biochemically low 25(OH)D without evidence of associated biochemical perturbation (for example raised PTH or low serum calcium) contributes to either increased fracture risk or impaired bone mineralisation in the growing skeleton is inconsistent. Importantly, much of the available data are from observational studies, and therefore, particular attention needs to be given towards confounding, the potential for reverse causality and the interpretation of a one off measure of 25(OH)D. Outdoor leisure time, physical activity and adiposity are a number of factors which can determine 25(OH)D but will also modify fracture risk and could potentially affect BMD. There is a suggestion from cross-sectional studies that very low levels of 25(OH)D might impact negatively on bone mineralisation during growth. This is supported by a recent meta-analysis, which suggested vitamin D supplementation might improve BMD in children and adolescents with the lowest levels of serum 25(OH)D but was of borderline statistical significance [106]; a beneficial effect on fracture reduction, however, remains to be demonstrated.

It is important that health care providers recognise that there is little evidence to support the concept of a low serum 25(OH)D concentration being a disease in itself [111]. Low levels of serum 25(OH)D without elevations in PTH or ALP are common in the general population, and equating such findings with a detriment to skeletal development at the individual level is problematic. One third of children will sustain a fracture during childhood [37], and as such, there is a high probability that low serum 25(OH)D and fracture will co-exist in a large number of children. There are no intervention studies which have examined fracture incidence in children who have received vitamin D supplementation, and the large

participant numbers and duration of observation required would likely make undertaking such a study unfeasible.

There is a lack of consensus on the serum 25(OH)D that reflects optimal status. Most proposed definitions are based on the prevention of secondary hyperparathyroidism, severe metabolic bone disease and hypocalcaemia. Although many clinical outcomes, including fracture and low BMD, have been linked with low circulating 25(OH)D, this remains an appropriate strategy in the absence of the definitive documentation of truly causal associations for such other conditions. Indeed, taken in the round, a threshold of 25 nmol/l for deficiency, as suggested by the British Paediatric and Adolescent Bone Group [25], appears likely to prevent most cases of VDD rickets [28].

In conclusion, despite the suggestion of a secular increase in the incidence of rickets, this observation may be driven more by changes in population demographics that a true alteration to age, sex and ethnicity-specific incidence rates; indeed, rickets remains uncommon overall and is rarely documented in fair-skinned children. Furthermore, there is scant evidence to support the notion that low serum 25(OH)D concentration per se is a risk factor for fracture or reduced BMD during growth. As such, the current evidence base does not support the routine assessment of serum 25(OH)D concentration or the recommendation of high-dose vitamin D supplementation in children with an acute fracture who are at low risk of VDD and not displaying overt signs of rickets or biochemical disturbance.

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