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ORIGINAL STUDY

Vitamin D : a poor screening tool for biochemical and radiological rickets

Giles T. FOLEY, Edward W. YATES, Farokh WADIA, Robin W. PATON

From East Lancashire Hospitals NHS Trust, Blackburn, Lancashire, UK

This retrospective study aims to determine if a relationship exists between serum 25-hydroxyvitamin D level and the diagnosis of biochemical or radiological rickets in children with bone and joint pain, muscle fatigue or varus/valgus knees. A retrospective biochemistry database and case note study was undertaken on 115 new patients referred to the senior authors' elective Paediatric Orthopaedic Clinic in 2010. Their mean age was 10.95 years (95% CI 10.24-11.68). Mean serum vitamin D was 18.27 mcg/l (95% CI 16.13-20.41), while 30 mcg/l is the normal threshold. One hundred and three children (88%) had vitamin D levels below normal. Winter/springtime blood samples were more likely to be deficient and this was statistically significant. Three Asian females (2.61%) were diagnosed with radiological rickets. Vitamin D levels below normal are common in children presenting with vague limb or back pain, but this rarely presents with biochemical or radiological rickets. Serum vitamin D level is not a suitable screening tool for biochemical or radiological rickets. Vitamin D requirement in children is unclear and requires further study.

Keywords : serum 25-hydroxyvitamin D ; rickets.

INTRODUCTION

Serum vitamin D is most accurately determined by assay of serum 25-hydroxyvitamin D, a precursor of the active form 1,25-dihydroxyvitamin D_3 (1,25-OH_2D_3), also known as calcitriol (*15*). An expert consensus (*15*) is developing that *optimal vitamin D status*, reflected by optimal calcium handling and best health, means a serum concentration of 25-OH vitamin D equal to or above 30 mcg/l.

In recent years there has been a noticeable increase in the volume of media coverage regarding childhood vitamin D deficiency and rickets (*7,8,9, 10,11*). Studies from the USA have described a prevalence of *relative deficiency* in children from 40% to 90% (*2,14*) below an accepted optimal threshold of 30 mcg/l. The prevalence was 12.1% if *true deficiency* (≤ 20 ng/mL) was considered (*2*).

Risk factors for Vitamin D deficiency include dark-skin (with greater levels of ultraviolet B (UVB)-absorbing melanin), skin-concealing attire, living above 40 degrees of latitude (*16*), vegetarian diet, and being exclusively breast-fed (*15*).

■ Giles T. Foley, MBChB, Specialist Registrar.
■ Edward W. Yates, MBChB, Specialist Registrar.
■ Farokh Wadia, MBChB, Specialist Registrar.
■ Robin W. Paton, MBChB PhD, Consultant Orthopaedic surgeon, Honorary Senior Lecturer, University of Manchester.
Dept of Orthopaedics, East Lancashire Hospitals, NHS Trust, Royal Blackburn Hospital, Blackburn, Lancashire, UK.
Correspondence : Giles T Foley, MBChB, c/o Mrs Sheila Dunn, Dept of Orthopaedics, East Lancashire Hospitals, NHS Trust, Royal Blackburn Hospital, Haslingden Road, Blackburn, Lancashire, BB2 3HH, UK.
E-mail : gilestfoley@me.com

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Vitamin D is a critical factor in bone metabolism (*14*) through its physiologically-active derivative 1,25-dihydroxy vitamin D. There are very few dietary sources of vitamin D : oily fish, eggs, margarines and some breakfast cereals. The principal source of vitamin D is cutaneous synthesis utilising solar ultraviolet B radiation (*1*).

MATERIALS AND METHODS

From January 1 to December 31, 2010, serum 25-hydroxyvitamin D levels were measured in all children attending elective paediatric orthopaedic clinics at the Royal Blackburn Hospital (region of North West England) with complaints of joint pain, leg pain, back pain, muscle fatigue and certain acquired limb deformities (varus and valgus knee joints). In the majority of children, parathyroid hormone (PTH), adjusted calcium and alkaline phosphatase levels were also measured, in order to identify biochemical rickets. All children had radiographs of their symptomatic or deformed limb, joint or spine.

A retrospective case note and biochemistry database review was performed for each child. Vitamin D deficiency was determined according to accepted laboratory 25-hydroxyvitamin D thresholds (*15*) : 30 mcg/l was the limit. *Biochemical rickets* was diagnosed when a low vitamin D titre was found in association with an elevated PTH level. *Radiological rickets* was diagnosed when thickened and widened physes, metaphyseal cupping, diaphyseal bowing or blurred trabecular architecture were evident on plain radiographs (Fig. 1). The senior author reviewed all radiographs to determine the presence or absence of radiological rickets. Exclusion criteria included individuals less than 12 months and over 16 years of age, those with inadequate radiographs and those with underlying skeletal dysplasias or syndromes. Seasons were defined as spring (March to May inclusive), summer (June to August), autumn (September to November) and winter (December to February) (*12*). Sensitivity, specificity, positive predictive value, negative predictive value and odds ratios with a 95% confidence interval were calculated. Statistical analysis was performed using Stats Direct (Stats Direct, Altrincham, UK).

RESULTS

The records of 115 children were analysed. Their mean age was 10.95 years (95% confidence interval 10.24-11.68). Sixty-three children were female and

Fig. 1. — Typical radiographic hallmarks of rickets : physeal broadening and thickening, physeal cupping and bilateral genu varum.

52 were male. Fifty-one were of Asian ethnicity and the remaining 64 were of Caucasian ethnicity.

Prevalence of low vitamine D levels

One hundred and three children (89.6%) had Vitamin D levels regarded to be subnormal (Table I). Their mean vitamin D level was 18.27 mcg/l (95% confidence interval 16.13-20.41), or below the limit of 30 mcg/l, and thus defined as 'insufficient'.

Vitamin D deficiency versus gender, ethnicity, and season

Males and children of Asian origin were more likely to be deficient than their female and Caucasian counterparts respectively, though this was not statistically significant (Table II). Winter or springtime blood tests were more likely to be deficient than those taken in summer or autumn, and this was statistically significant (Table II).

Vitamin D deficiency and pain

Pain was a presenting complaint in 97 children (84.3%), though paradoxically this was more common in children with normal vitamin D levels (Table IIIa). The commonest site of pain was in the

Table I. — Various thresholds of vitamin D levels

vitamin D level (mcg/l)	No. of children (%)	mean age (years) (95% CI)
< 10 (deficient)	28 (24.3)	13.11 (11.90-14.32)
10-19.9 (insufficient)	48 (41.7)	10.50 (9.45-11.55)
20-29.9 (suboptimal)	27 (23.5)	10.11 (8.36-11.86)
≥ 30 (normal)	12 (10.4)	9.58 (7.74-11.42)

Table II. — Vitamin D as a function of gender, ethnicity, and season

Probability of male being vitamin D deficient	92.31%
Probability of a female being vitamin D deficient	87.30%
Odds of a male being vitamin D deficient	12.00
Odds of a female being vitamin D deficient	6.88
Odds ratio (95% CI)	1.75 (0.46-6.16)
Probability of an Asian being vitamin D deficient	96.08%
Probability of a Caucasian being vitamin D deficient	84.38%
Odds of an Asian being vitamin D deficient	24.50
Odds of a Caucasian being vitamin D deficient	5.40
Odds ratio (95% CI)	4.54 (0.95-21.74)
Probability of a summer/autumn test being vitamin D deficient	82.76%
Probability of a winter/spring test being vitamin D deficient	96.49%
Odds of a summer/autumn test being vitamin D deficient	4.80
Odds of a winter/spring being vitamin D deficient	27.50
Odds ratio (95% CI)	5.73 (1.20-27.45)*

(*statistically significant).

lower limbs (76.2%), while spine pain (20.2%) and upper limb pain (3.6%) were less prevalent (Table IIIb).

Vitamin D deficiency and radiological rickets

In total, three children (2.61%) were diagnosed with radiological rickets. These children were Asian females aged 4, 4 and 15 years respectively. The vitamin D levels were 2.2, 8.3 and 12.4 mcg/l, quite below the limit of 30 mcg/l. The titres had been measured in winter, spring and summer respectively. Although 28 children (24%) had less than 10 mcg/l, only 2 of these presented with radiological rickets. Again, 76 or 66% of the children had a vitamin D level less than 20 mcg/l and only 3 presented with radiological rickets. So the association between the level of serum vitamin D and radiological rickets was poor. There were good sensitivity and negative predictive values (both 100%), when the threshold was set at 20 mcg/l, but poor specificity and positive predictive values (Table IV). Positive predictive values were poor at all thresholds : 10,15, 20 and 30 mcg/l. These results may be affected by the low incidence of radiological rickets.

Vitamin D deficiency and biochemical rickets

A subgroup of 80 children had parathyroid hormone (PTH) levels measured in addition to vitamin D titres. Forty-six were female, the mean age of the subgroup was 11.25 years (95% Confidence Interval 10.39-12.11) and the mean PTH was 57.89 ng/l (95% Confidence Interval 35.23-80.65) (normal range 12-65 ng/l). Fifteen children (18.8%) had a raised PTH level. The association between serum vitamin D concentration and biochemical rickets was also poor. The positive predictive value and specificity were low, reflecting the number of false-positives (Table V). Adjusted serum calcium and alkaline phosphatase levels were normal in all but one child, who had a vitamin D level of 2.2 mcg/l

Table III. — a : pain and b : pain localisation : correlation with vitamine D

Vitamin D status	No. of children	Presented with pain	Presented without pain	Proportion with pain
Deficient	103	86	17	83.5%
Normal	12	11	1	91.7%

Site of pain	No. of children (86 with pain) (2 excluded because of pain in 2 regions)	mean vitamin D (mcg/l) (95% CI)
Upper limb	3	24.0 (16.1-31.9)
Lower limb	64	15.1 (13.4-16.8)
Spine	17	15.0 (11.7-18.3)

and a PTH level of 912 pg/ml (normal range, 12-65). This child was also diagnosed with radiological rickets.

DISCUSSION

The authors found a statistically significant difference between the serum 25-hydroxyvitamin D levels recorded in the summer/autumn months and the winter/spring months. Blackburn (region of North West England) is often overcast, with 1300-1350 mean hours of sunshine per year, which compares unfavourably to more southern areas of the United Kingdom, such as Cowes (Isle of Wight) (1750-1900 mean hours) (*13*). An integral stage in cutaneous Vitamin D production is the photolysis of 7-dehydrocholesterol to Pre-Vitamin D-3 by ultraviolet blue light. This only occurs above an ultraviolet radiation threshold of 18 mJ/cm^2 (*6*). Generally, during winter months, this exposure level is not reached in the northern hemisphere above 40° latitude (*4*) (Blackburn is situated at 53.7° North latitude) (*6*). Accordingly, it is likely that geographical latitude and sunshine hours are important in the aetiology of vitamin D deficiency.

The authors found that vitamin D levels have a strong sensitivity but a poor specificity when predicting radiological rickets (Table IV). Again, vitamin D levels are fairly sensitive but poorly specific when screening for biochemical rickets (Table V). Vitamin D measurement has persistently poor positive predictive values for both biochemical and radiological rickets as a consequence of high false positive rates. This suggests that serum 25-hydroxy-vitamin D would not be a suitable screening test for rickets according to Wilson and Jungner's criteria (*16*). Measuring the physiologically active 1,25-dihydroxyvitamin D might prove more accurate.

Table IV. — Vitamin D : predictive values for radiological rickets as a function of varying deficiency thresholds

Vitamin D deficiency threshold : 30 mcg/l	
Sensitivity	100%
Specificity	10.71%
Positive predictive value	2.91%
Negative predictive value	100%
Vitamin D deficiency threshold : 20 mcg/l	
Sensitivity	100%
Specificity	34.82%
Positive predictive value	3.95%
Negative predictive value	100%
Vitamin D deficiency threshold : 15 mcg/l	
Sensitivity	100%
Specificity	50.89%
Positive predictive value	5.17%
Negative predictive value	100%
Vitamin D deficiency threshold : 10 mcg/l	
Sensitivity	66.67%
Specificity	76.79%
Positive predictive value	7.14%
Negative predictive value	98.90%

The current study also suggests that normal bony radiographic appearances are not indicative of satisfactory vitamin D nutrition and good bone health. One hundred of 103 children (97%) with below normal vitamin D levels had normal radiographs. This might be explained as follows : children's bone growth is not linear, and therefore a child's demands for vitamin D might vary accordingly. We

Table V. — Vitamin D : predictive values for biochemical rickets with a deficiency threshold of 20 mcg/l

Sensitivity	78.57%
Specificity	40.91%
Positive predictive value	22%
Negative predictive value	90%

have shown that low levels of vitamin D often do not result in radiological or biochemical rickets. Perhaps, therefore, children can tolerate these low vitamin D levels outside periods of rapid growth without developing skeletal abnormalities. Interestingly, our 3 cases of radiological rickets were aged 4, 4 and 15, which corresponds with the ends of the infantile and adolescent growth spurts. Alternatively, our thresholds for diagnosis may be inaccurate.

Currently thresholds for childhood vitamin D deficiency are considered to be the same as in adults. The normal adult threshold is defined as the minimal serological level to maintain a normal parathyroid hormone (PTH) titre (*14*). In adults, the relationship between vitamin D and PTH is sigmoid, whereas in children it is linear (*3*). This physiological difference may make the use of adult values inaccurate in children.

Rickets is becoming more common in our paediatric populations. Vitamin D appears to be deficient amongst most children attending Paediatric Orthopaedic Clinics with non-specific limb and spinal complaints. Despite this, very few suffer biochemical or radiological rickets. Serum 25-hydroxyvitamin D measurement does not appear to be a reliable screening tool for radiological or biochemical rickets. Normal radiographs do not suggest adequate vitamin D nutrition. Research is required to establish normal paediatric serum vitamin D concentrations, which may need adjustment for age to reflect periods of amplified bone growth, when demand for vitamin D would be expected to increase.

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