

Vitamin D status in Irish infants

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Abstract

Vitamin D is essential for good bone health particularly during infancy, a time of rapid growth. Given Ireland's northerly latitude, Irish children are at risk of suboptimal vitamin D levels. The aim of our study was to describe the vitamin D status of a group of Irish infants and identify factors predictive of vitamin D status. A cross-sectional study was undertaken over a 12-month period in a single paediatric tertiary referral centre in Dublin. Fifty-four healthy term infants (<1 year of age) attending a single hospital for minor medical or surgical procedures were recruited. All patients had measurement of serum 25-hydroxyvitamin D (25OHD), parathyroid hormone (PTH) and a bone profile. A questionnaire detailing vitamin D intake from diet, vitamin D supplementation and sun exposure was completed on behalf of each participant. The mean (SD) for serum 25OHD was 80.8 (34.4) nmol/L and almost 80% of infants had 25OHD levels >50 nmol/L. Lower serum 25OHD levels were seen in the following: breastfed infants, infants with formula consumption of <500ml per day, darker skin and no vitamin D supplementation. In our study, most infants have 25OHD levels in the range for optimal skeletal development, above 50 nmol/L, but important risk factors for suboptimal serum 25OHD levels have been identified and will aid in identifying those infants most at risk.

Key words: Ireland, Vitamin D, Infant, 25-OH vitamin D

1. Introduction

Infancy is a time of rapid linear growth and vitamin D is essential for good bone health as it plays a fundamental role in bone metabolism and calcium homeostasis. Severe deficiency manifests itself clinically with rickets (1). Infants are at particular risk of low serum 25 hydroxyvitamin D (25OHD) levels in comparison to older children or adults. Firstly, it is recommended that they avoid direct exposure to sunlight, the major endogenous source of cholecalciferol (vitamin D₃) (2). Secondly, the few natural food sources of vitamin D, such as oily fish and eggs, are not commonly part of infant diets. Finally, while formula milk is fortified with vitamin D and contains on average 480 IU/L of vitamin D₃, the vitamin D content of breast milk is lower (25-78 IU/L), even when lactating mothers are supplemented with vitamin D daily (3, 4).

A Cochrane review from 2006 agreed that vitamin D supplementation of infants and toddlers was appropriate as a measure to prevent nutritional rickets (5). Both the American Academy of Pediatrics (AAP) and the Lawson Wilkins Pediatric Endocrine Society (LWS) recommend vitamin D supplementation of 400 IU per day for all infants, unless they are consuming more than 1 litre of fortified formula milk per day (6, 7). The Institute of Medicine (IOM) also recommends an adequate intake of 400 IU of vitamin D per day in infancy (8). Most European countries have adopted similar policies for vitamin D supplementation in infancy, with the majority recommending 400 IU of vitamin D once a day (9).

In June 2010, a national policy recommending supplementation of all Irish infants from birth to 12 months with 200 IU daily of vitamin D₃ irrespective of whether breastfeeding or formula feeding was implemented (9, 10). While this policy was in keeping with international recommendations, no data describing the vitamin D status of Irish term infants was available prior to its introduction. A study of preterm Irish infants has since found that up to 78% of them had 25OHD levels below 50 nmol/L (11).

Vitamin D has a number of extraskeletal roles; vitamin D receptors are found in many tissues and cells of the body that are unrelated to calcium and bone metabolism (12). Vitamin D is an immunomodulator and supplementation in infancy has been associated with a reduced incidence of developing type 1 diabetes mellitus, an autoimmune condition (13, 14). Increased susceptibility to infection at lower serum 25OHD levels has been reported but a randomised controlled trial in young children has failed to support this finding (15-18).

The optimal 25OHD level for skeletal and extraskeletal health remains a topic for debate. Position statements from two paediatric bone groups have recommended that the target 25OHD level for optimal bone health in infants, children and adolescents is ≥ 50 nmol/L (19, 20). It is generally accepted that vitamin D deficient rickets, in the setting of a normal calcium intake, does not occur if the serum 25OHD level is above 30 nmol/L and often only at levels below 12.5 nmol/L (1, 20, 21).

Supplementing Irish infants with vitamin D should optimise bone health and avoid privational

rickets. Supplemented infants may also benefit from possible extraskkeletal benefits of vitamin D in the short and long term. The aim of this study was to describe the vitamin D status of a group of healthy Irish term infants and identify factors predictive of vitamin D status.

2 Experimental methods

2.1 Patient group

Ethical approval for the study was granted by the Scientific and Ethics Committee of the Children's University Hospital. Written informed parental consent was given in all cases. We performed a cross sectional study over a 12-month period from March 2010 – March 2011. We recruited healthy term infants, born in Ireland, attending the Children's University Hospital for elective surgery (26%), medical outpatients (62%) or the emergency department (12%) for a minor complaint. Children with complex disorders likely to affect vitamin D intake or absorption or known metabolic bone disease were excluded. All children were having phlebotomy performed for a clinical indication.

2.2 Questionnaire

A questionnaire was completed on behalf of each patient enrolled in the study detailing vitamin D intake from diet, vitamin D supplementation and sun exposure. Weekly intake of vitamin D rich foods (oily fish and eggs) was documented as well as daily milk consumption and the use of formula milk. The use of vitamin D supplements and multivitamins over the previous 3 months was noted. The implementation of the national policy

recommending vitamin D supplementation occurred midway through the study period. Sun exposure over the previous week was recorded, including the use of sunscreen. The ethnicity of the child was determined using the Health Service Executive Ethnic Identifier in addition to the parents' country of origin. The presence of any medical condition, use of medications and reason for attendance at hospital was documented.

2.3 Laboratory measurements

Whole blood (3.5 ml) was taken in serum bottles from each patient. Serum 25OHD, PTH and a bone profile (calcium, phosphate, alkaline phosphatase, albumin and urea) were measured. Total 25OHD (25OHD₂ and 25OHD₃) was measured by liquid chromatography tandem mass spectrometry. The assay has an intra-assay CV of 5% and an inter-assay CV of 7%. Vitamin D levels are expressed as total vitamin D. Serum PTH assay was measured using a solid-phase two-site chemiluminescent immunoassay, performed on the Immulite™ 2000. The assay has an intra-assay CV of 5% and an inter-assay CV of 4%. Bone profiles were performed on the Beckman Coulter DXC 600 Analyser.

2.4 Interpretation of vitamin D status

Serum 25OHD levels were interpreted according to the 2011 Institute of Medicine report as follows: a serum 25OHD level below 30 nmol/L (12ng/ml) was defined as being at increased risk of vitamin D deficiency; a level of 30-to-50 nmol/L (12-20 ng/ml) as within the range of adequacy, and >50 nmol/L (20 ng/ml) as sufficient. All patients with serum 25OHD <50 nmol/L were informed of

the result and supplementation with 200 IU (5µg) of vitamin D₃ was recommended for 3 months along with other measures to improve vitamin D intake.

2.5 Statistical analysis

Results are presented as mean and standard deviation (SD) or as number and percentage. Serum 25OHD levels were normally distributed. Serum 25OHD was analysed as a continuous variable and its association with other variables was examined using independent t-tests if two groups were present and ANOVA if 3 or more groups were present. The association between serum 25OHD and indices of calcium metabolism was analysed by Pearson's correlation coefficient. The total group was divided into two categories of vitamin D status based on a 25OHD threshold of >50 nmol/L; the relationship with other categorical variables was tested by Chi-square. Significance was defined as $p < 0.05$. Statistical analysis was conducted using IBM SPSS Stats for Windows Version 20 (Armonk, New York).

3 Results

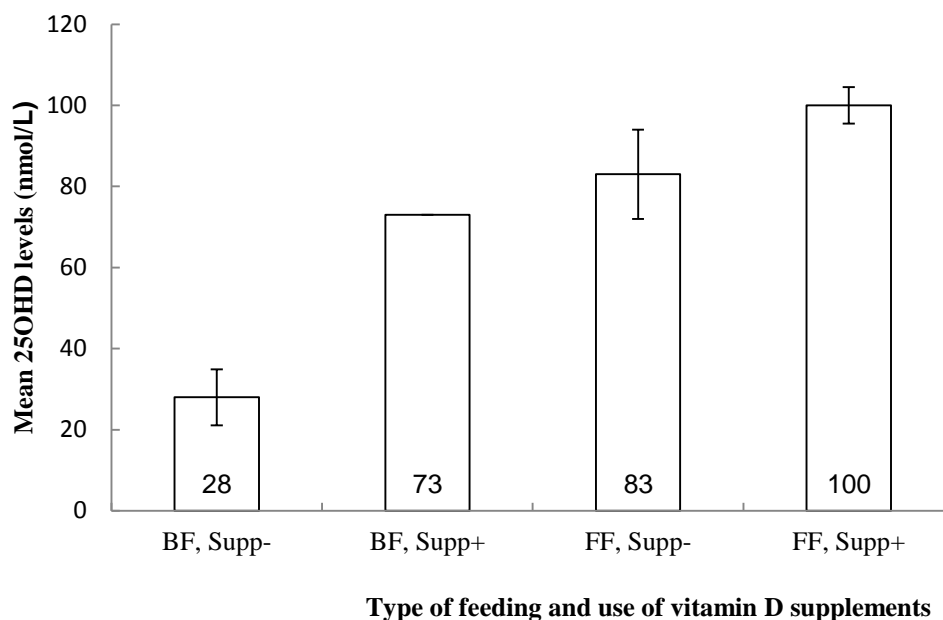
We studied 54 term infants; the median age was 0.58 years (range 0.06-0.98 years); there were 26 females and 28 males; ethnicities included white Irish, white European and Asian. The mean (SD) for serum 25OHD was 80.8 (34.4) nmol/L; 7.4% had serum 25OHD levels below 30 nmol/L (at-risk of vitamin D deficiency), 13% in the range of adequacy (30-50 nmol/L) and 79.6% had levels above the threshold for sufficiency (>50 nmol/L). Descriptive statistics of measured bone indices (calcium, phosphate, alkaline phosphatase and parathyroid hormone (PTH)) are shown in Table 1. Serum 25OHD levels correlated inversely with PTH ($r = -0.335$, $p = 0.019$) while calcium ($r = 0.342$, $p = 0.015$) showed a positive correlation with 25OHD. There was no correlation between phosphate ($r = 0.228$, $p = 0.111$) or alkaline phosphatase ($r = -0.131$, $p = 0.363$) and 25OHD.

Table 1: Descriptive statistics of laboratory measurements in all infants

Variable	Mean	SD	Range
25OHD (nmol/L)	80.8	34.4	10.0-149.8
PTH (ng/L)	45.2	145.5	3.0-1023.7
Calcium (mmol/L)	2.49	0.11	2.05-2.74
Phosphate (mmol/L)	1.95	0.25	0.84-2.43
Alk Phos (U/L)	363	603	118-4240

Infants consuming formula milk had mean (SD) serum 25OHD levels more than double those of breastfed infants (87.5 (30.7) versus 34.6 (23.1) nmol/L, $p < 0.001$) (Figure 1) (Table 2).

Figure 1: Mean 25OHD levels in relation to type of feeding and use of supplements.



25OHD, 25-hydroxyvitamin D; BF, breast fed; FF, formula fed; Supp -, no vitamin D supplementation; Supp+, vitamin D supplementation.

Mean 25OHD value displayed at base of column. Standard error of the mean illustrated by error bars. No error bar in BF, Supp + as only 1 patient in that group.

Infants who consumed ≥ 500 ml of formula milk per day had significantly higher serum 25OHD levels than those consuming < 500 ml ($p=0.023$) (Table 2). Almost 30% of infants were receiving vitamin D supplementation and this significantly increased the mean (SD) serum 25OHD levels from 73.8 (31.3) nmol/L in the unsupplemented group to 98.5 (39.3) nmol/L in the supplemented group

($p=0.025$). Of the infants receiving vitamin D supplementation, 92% had 25OHD levels above 50 nmol/L. Consumption of other dietary sources of vitamin D did not significantly affect serum 25OHD levels. Ethnicity significantly affected vitamin D status. Children of Asian ethnicity had significantly lower mean 25OHD levels than white Irish or other European children ($p=0.038$).

Table 2: Descriptive statistics of factors associated with vitamin D status

Factor	Characteristic	n	%	Mean 25OHD	SD	P
All		54	100	80.8	34.4	
Sex	Female	26	48	83.2	41.1	0.470
	Male	28	52	76.2	28.5	
Age	< 6 months	24	44	72.5	38.1	0.225
	≥ 6 months	30	56	84.6	32.1	
Health insurance	Yes	12	22	76.2	28.3	0.708
	No	42	78	80.5	27.5	
Ethnicity	Non-Asian	43	83	84.2	32.0	0.038*
	Asian	9	17	58.0	40.7	
Supplements	Yes	14	29	98.5	39.3	0.025*
	No	35	71	73.8	31.3	
Milk type	Breastfed	7	14	34.6	23.1	<0.001*
	Formula	44	86	87.5	30.7	
Milk intake (ml/day)	<500	12	27	67.0	28.3	0.023*
	≥500	33	73	91.2	32.9	
Egg intake/wk	Never	10	20	77.4	35.0	0.235
	<3	41	80	92.1	33.4	
Oily fish intake/wk	<1	41	82	79.9	36.3	0.653
	≥1	9	18	85.1	29.0	
Season	April/Sept	27	50	73.1	33.2	0.181
	Oct/Mar	27	50	86.0	36.1	
Sunscreen use	Yes	15	40	86.4	25.9	0.656
	No	22	60	80.7	44.1	
Sun exposure/day	<30 mins	33	70	76.9	37.5	0.234
	≥30 mins	14	30	89.2	28.8	

25OHD, 25-hydroxyvitamin D

*Mean value was different between the two groups

Vitamin D status did not change significantly by infant age, gender, time spent outdoors, sunscreen use or health insurance, a surrogate marker of socioeconomic status. Vitamin D status did not change significantly by season. The mean (SD) 25OHD levels for January-March, April-June, July-September and October – December were 71.1 (26.7), 66.7 (28.6), 74.6 (34.6) and 94.2 (38.7) nmol/L, respectively.

There was a non-significant trend for the prevalence of vitamin D supplementation to be

more common in the second half of the study period, following implementation of the national vitamin D supplementation policy, compared to the first half (p=0.169). In infants with the lowest and highest serum 25OHD levels, use of vitamin D supplementation and feeding type were examined (Table 3). Those with the highest serum 25OHD levels were all formula fed while those with the lowest values were all breastfed.

Table 3: Type of feeding type, milk volume and supplementation use in the infants with the highest and lowest 25OHD levels.

Age (years)	25OHD level (nmol/L)	Feeding type	Milk per day (ml)	Supplementation
0.94	10.0	BF	NA	No
0.06	12.6	BF	NA	No
0.29	21.4	BF	NA	No
0.06	34.7	BF	NA	No
0.21	126	FF	500-1000ml	No
0.59	138.4	FF	500-1000ml	No
0.98	146.2	FF	500-1000ml	No
0.78	149.8	FF	500-1000ml	Yes

25OHD, 25 hydroxyvitamin D; BF, breast fed; FF, formula fed; NA, not available

4 Discussion

This is the first study describing the vitamin D status of a group of healthy Irish term infants. Almost 80% of whom had serum 25OHD levels at or above the threshold for sufficiency (50 nmol/L) despite the fact that only one third of them were taking vitamin D supplements. The type of feeding, quantity of formula milk consumed, use of vitamin D supplements and ethnicity all had a significant effect on serum 25OHD levels.

As expected, unsupplemented breastfed infants had lower mean serum 25OHD levels than formula fed infants with or without vitamin D supplementation, in keeping with previous reports (22-24). Only one of the breastfed infants was supplemented and this infant had a serum 25OHD level of 73 nmol/L. Supplementation of breastfed infants with 400 IU of vitamin D₃ has been shown to maintain 25OHD levels above 50 nmol/L without

adverse events but has not been shown to be superior to 200-250 IU(25-29). In order to achieve a serum 25OHD level ≥ 75 nmol/L, high dose vitamin D supplementation of breast fed infants has been examined (25). Vitamin D₃ dosages of 400, 800, 1200 and 1600 IU have been compared; at 3 months the mean serum 25OHD levels in the 4 groups were 78, 102, 134 and 180 nmol/L, respectively. The 1600 IU dosage was discontinued because most infants in this group developed elevated serum 25OHD concentrations that have been associated with hypercalcaemia. Similar serum 25OHD levels were reported in a similar study in which infants were supplemented with 250, 750 or 1000 IU of vitamin D₃ (30). The 2011 IOM report established a safe range above the range of adequacy from 50-125 nmol/L and set tolerable upper intake levels for infants aged 0-6 months of 1000 IU/day, and for those aged 6-12 months of 1500 IU/day(8).

Most infants in this study were formula fed. Breast feeding rates in Ireland are among the lowest in Europe (31) but initiatives by the health service are aiming to improve these rates (32, 33). Consumption of formula milk led to higher vitamin D levels as expected, given the vitamin D fortification of this product.

Four months into the 12-month study period (June 2010), the policy on vitamin D supplementation for infants in Ireland was implemented. The percentage of infants receiving vitamin D supplements increased but not significantly in the second half of the study period ($p=0.169$). This reflects the recent introduction of the policy. Poor adherence to vitamin D supplementation policies in children has been recognised in Ireland and other European countries (34-36).

We demonstrated a significant effect of ethnicity on vitamin D status. Darker skin colour is a well-recognised risk factor for vitamin D deficiency as melanin absorbs ultraviolet B photons, which reduce the endogenous production of vitamin D. In a review of 166 cases of nutritional rickets in the United States, 83% of children were described as African American or black (24). We observed no seasonal variation in serum 25OHD levels in infancy; this is not surprising as it is recommended that infants, particularly less than six months of age, are not exposed to direct sunlight and is consistent with other studies (22, 29).

One case of rickets was identified in an unsupplemented breastfed infant of Asian ethnicity aged 11 months. This patient had a serum 25OHD

level of 10 nmol/L with calcium within the normal range (2.40 mmol/L), a low phosphate level (0.84 mmol/L) and a raised alkaline phosphatase (1385 U/L) and PTH (1023 ng/L).

The relatively small sample size may be seen as a limitation of this study. However, this group of patients had an equal sex distribution, included infants from across the country at various stages of infancy and had an ethnicity profile in keeping with that of the general population.

Most Irish infants had serum 25OHD levels in the target range, which is ideal for good bone health. Unsupplemented breast-fed infants and those with darker skin colour were most at risk of vitamin D deficiency and these at risk groups should be particularly targeted by healthcare professionals in Ireland when discussing vitamin D supplementation.

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5.2 Conflict of Interest

None

5.3 Contributorship

AC and NM designed the study, obtained funding and ethical approval and recruited patients. AC and MJM analyzed the data. AC wrote the manuscript. CO and EJM assisted with design and implementation of the study.

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