Original Article

Natural history of infants with vitamin D deficiency in Hong Kong

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Background and Objectives: The usual recommended intake of vitamin D for healthy infants is 400 international unit (IU) daily. However, a high dose of vitamin D at 2000-3000 IU daily is needed for those with vitamin D deficiency (VDD). This study aimed to assess the natural history of a group of healthy infants with VDD and the associated factors for persistent VDD. **Methods and Study Design:** Healthy infants detected to have VDD (25OHD <25 nmol/L) in a population study were followed, and their demographics and clinical data were collected. **Results:** One hundred and thirty-one subjects (boys = 66%) were included. Their first serum 25OHD was taken at a median age of 87.5 days. None were treated with high-dose vitamin D supplements, but some have been given vitamin D at 400 IU daily. They were assessed again at the median age of 252.5 days when 15 remained to have VDD and 26 were in the insufficient range (25 - 49.9nmol/L). All persistent VDD children were on exclusive breastfeeding. Exclusive breastfeeding and no vitamin D supplementation were significant risk factors for persistent vitamin D insufficiency (<50nmol/L). **Conclusions:** Persistent VDD is common among infants exclusively breastfeeding and those who did not receive vitamin D supplementation.

Key Words: vitamin D, serum 25-hydroxyvitamin D, infants, rickets

INTRODUCTION

Vitamin D is an essential micronutrient that regulates calcium and phosphate metabolism. Globally, the prevalence of vitamin D deficiency was higher in African, Asian, Turkish and Moroccan children than those of a western ethnic background.[1] The great variation of the prevalence of vitamin D deficiency is a result of huge variations in geographical locations, seasons, skin pigmentation and diet of study subjects,[2] which affects the vitamin D synthesis (via ultraviolet B irradiation from sunlight) and the uptake of vitamin D (via food intake, e.g. from liver, egg-yolk, and fatty fish, or fortified milk, margarine, butter and infant formulas). Several previous studies have reported the situation of vitamin D deficiency and insufficiency among infants and pregnant women in Hong Kong.[3–5] From an earlier pilot study on a small sample in Hong Kong, 22% and 34% of infants at 3 months of age were found to have vitamin D deficiency (<25 nmol/L) and insufficiency (<50 nmol/L) respectively; and the prevalence of vitamin D deficiency was significantly higher among exclusively breastfed infants.[3] The usual recommended intake of vitamin D for healthy infants is 400 IU daily, while high dose vitamin D at 2000-

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3000 IU daily is needed for infants and toddler with vitamin D deficiency.[6] A relevant clinical question is whether serum 25-hydroxyvitamin D (25OHD) concentrations in infants should be measured to determine the optimal dosing of vitamin D supplementation.

With various multi-sectoral breastfeeding promotion strategies including the Baby Friendly Hospital Initiative in Hong Kong, the rate of exclusive breastfeeding rate till 6 months of age increased from 8% in 2000 to 22% in 2020.[7] The benefits of breastfeeding are well known, and it is unquestionable that breast milk provides the most optimal nutrients for infants. Nevertheless, human breastmilk is a poor source of vitamin D, and infants on exclusive breastfeeding would not be able to acquire their daily vitamin D requirement from breast milk alone.[8,9] Therefore, vitamin D supplementation for infants, especially those on exclusive breastfeeding, has been recommended by various professional bodies.[6,10] However, with ethnic and geographic variations, implementations of these recommendations should be adapted based on the local data. In Hong Kong, there is no local guideline on vitamin D supplementation for infants, including those receiving exclusive breastfeeding. With that, in 2019, The Department of Health (DH) of the Hong Kong Special Administrative Region Government commissioned the Department of Paediatrics and Adolescent Medicine, The University of Hong Kong to conduct a study to assess the vitamin D status among infants, toddlers, and pregnant women in Hong Kong. In this study, healthy infants and toddlers were recruited from the maternal and child health centres (MCHCs) and antenatal clinics located in different districts in Hong Kong. Vitamin D status was defined based on the clinical practice guidelines of the Endocrine Society Task Force on Vitamin D.[11] Vitamin D deficiency (VDD) was defined as 25OHD concentration of less than 25 nmol/L and vitamin D insufficiency (VDI) was defined as a serum 25OHD concentration of 25-49.9 nmol/L. Infants and toddlers with VDI were advised to take over-the-counter vitamin D supplement at 400 IU daily for those younger than 12 months of age and 600 IU daily for those older than 12 months respectively. For those with VDD, they were referred to the Hong Kong Children's Hospital (HKCH) for further management and treatment with high dose vitamin D.

The objective of this study is to assess the natural history of this group of healthy infants with VDD and to investigate the factors contributing to persistent vitamin D deficiency and insufficiency.

METHODS

Participants

Eligible infants and toddlers were recruited at six major MCHCs located in six different districts and the antenatal clinics of seven hospitals in Hong Kong. Those who were seen between 1st January 2019 and 31st December 2021 were invited to join the study. Healthy neonates and infants participated in the current study were checked for their serum 25OHD using liquid chromatography-tandem mass spectrometry method, the current gold standard in vitamin D status assessment.[12] VDD were diagnosed in those with serum 25OHD <25 nmol/L (after subtraction of 3-epi-25(OH)D3 concentrations). These infants and toddlers were referred to HKCH for further management and were assessed by paediatric endocrinologists for any clinical sign of rickets. Serum concentration of 25OHD, calcium, phosphate and alkaline phosphatase (ALP) were repeated on the day of assessment in HKCH to confirm the vitamin D status. They would then be treated with high dose vitamin D (age 1-12 months: 2000 IU daily, >12 months: 3000 IU daily) for 3 months if they have persistent VDD. For those with VDI, they were given vitamin D 400 IU daily.

Body length was measured using an infantometer (seca 416, Deutschland) from the top of the head to the sole of the foot with the baby lying supine. The head of the infant was held in the Frankfurt horizontal position with the lower edge of the bony orbit and the ear positioned in the same vertical plane. The hips and knees were extended using gentle force. Body weight was measured using an electronic weighing scale (TANITA BD-585, Japan), which was accurate to 10 g and calibrated before each measurement. The height Z-score and weight Z-score were calculated according to the local reference.13 Patients' demographics and clinical data, including sign of rickets, anthropometric parameters, 25OHD concentrations, feeding mode, use of vitamin D supplementation were also collected. Infants with any major congenital malformations or genetic defects, being born premature, or with low birth weight were excluded from this study. In our study, we defined VDD as 25OHD <25 nmol/L, VDI as 25-49.9 nmol/L and vitamin D sufficiency (VDS) as 25OHD ≥50 nmol/L.

Ethics

The study was approved by the Research Ethics Committee of Hong Kong Children's Hospital (HKCH-REC-2021-054) and the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster Research Ethics Committee (UW 13-055). Written informed consent was obtained from each participant.

Statistical analysis

Descriptive statistics were reported as median (25th, 75th percentile). Proportions or percentages were used to describe the categorical data. Kruskal Wallis test and Chi-square test were used to analyse continuous and categorical variables as appropriate. Logistic regression analysis was used to adjust for potential confounders associated with 25OHD concentrations. All statistical tests were 2-sided and a p-value < 0.05 was considered statistically significant. Statistical Package for Social Sciences software for Windows (version 26.0, SPSS Inc., Chicago, IL, USA) was used for the statistical analysis.

RESULTS

One hundred and thirty-one subjects were included in this study (boys = 66%) (Table 1). Forty four of them were recruited in the 6 MCHCs and the rest was identified with cord blood sample from seven hospitals. Their first serum 25OHD was taken at a median age of 87.5 days. They were assessed again at the median age of 253 days in HKCH. None had been treated with high dose vitamin D

Table 1. Description of the subjects with and without vitamin D deficiency (25OHD <25 nmol/L) at follow-up

	Vit. D deficiency (<25nmol/L) (n = 15)	Vit. D insufficient (25 - <50nmol/L) (n = 26)	Vit. D sufficient (≥50nmol/L) (n = 90)	*p*
#Gender				1.00
Male, n (%)	10 (66.7)	17 (65.4)	59 (65.6)	
Female, n (%)	5 (33.3)	19 (34.6)	31 (34.4)	
Age (days) at FU, Median (IQR)†	247 (175-302)	237 (156-295)	202 (147-277)	0.03
Height, z-score, Median (IQR)†	0.4 (0.02-1.25)	0.3 (-0.06-0.97)	0.3 (-0.36-0.92)	0.88
Weight, z-score, Median (IQR)†	0.01 (-0.28-1.19)	-0.02 (-0.39-1.02)	0.2 (-0.44-1.11)	0.98
1st 25 Serum 25OHD (nmol/L), Median (TQR)†	14.7 (9.0-19.4)	21.3 (13.4-23.0)	19.2 (13.9-22.3)	0.03
FU interval (days), Median (IQR)†	124 (75-194)	116 (99-147)	150 (114-198)	0.12
Serum 25OHD (nmol/L), Median (IQR)†	15 (8.0-21)	40 (31-45)	77 (66-86)	<0.0001
Serum Ca, mmol/L, Median (IQR)†	2.5 (2.4-2.5)	2.5 (2.4-2.6)	2.5 (2.5-2.6)	0.004
Serum PO_4, mmol/L, Median (IQR)†	1.7 (1.6-1.7)	1.7 (1.7-1.9)	1.8 (1.7-1.9)	0.001
PTH, pmol/L, Median (IQR)†	4.1 (2.5-7.3)	2.3 (1.4-3.3)	2.0 (1.4-2.7)	<0.0001
ALP, u/L, Median (IQR)†	277 (259-291)	247 (215-279)	279 (217-324)	0.26
Vit. D supp (400 IU daily for at least 1 month)‡				0.04
Yes, n (%)	1 (7)	10 (39)	36 (40)	
No, n (%)	14 (94)	16 (61)	54 (60)	
Feeding modes‡				<0.0001
BF, n (%)	15 (100)	20 (77)	21 (23)	
Formula < 80%, n (%)	0	2 (8)	18 (20)	
Formula ≥ 80%, n (%)	0	4 (15)	51 (57)	

ALP: Alkaline phosphatase, BF: Breastfeeding, Ca: Calcium, FU: Follow-up, IQR: Interquartile range, IU: international unit, PO4: Phosphate, PTH: Parathyroid hormone, serum 25(OH)D: vitamin D, supp: supplement
†Chi-Square Test
‡Kruskal Wallis Test

before their first attendance at HKCH and some had taken over-the-counter vitamin D 400 IU daily.

At their first consultation at HKCH, 15 remained to be VDD (<25 nmol/L), while 26 were in the insufficient range (25-49.9 nmol/L). None had any clinical sign of rickets. Their mean height Z-score and weight Z-score were 0.4 (0.02 – 1.25) and 0.01 (-0.28 – 1.19), respectively. One girl had biochemical rickets. Her first serum 25OHD was checked at the age of 10 months and was 10nmol/L. Upon referral, her repeated serum 25OHD at 12 months of age was 8nmol/L. She was on exclusive breastfeeding and was not on any vitamin D supplements. She also had hypophosphatemia (phosphate: 1.3 mmol/L), hyperphosphatasia (ALP: 466 IU/L) and secondary hyperparathyroidism with high parathyroid hormone (PTH) at 9 pmol/L. Her body height Z-score was -2.0 and it was improved to -1.2 with high dose vitamin D treatments (2000 IU daily) for 3 months. Her serum 25OHD, phosphate, ALP and PTH were also normalized. Otherwise, she had no other clinical sign of rickets.

Comparing the group remained to have VDD vs. the non-VDD group (including insufficient and sufficient group) (Table 1), the non-VDD group had higher initial 25OHD concentration and they were more likely to have received over-the-counter vitamin D supplements (400 IU daily) for at least one month. There was no difference in terms of height and weight among the three groups including deficiency, insufficient and sufficient group (Table 1). All persistent VDD children were on exclusive breastfeeding. On the other hand, among the 56 children who were on exclusive breastfeeding, 27% had persistent VDD. Table 1 summarized the clinical characteristics of the three groups. Exclusive breastfeeding and no neonatal vitamin D supplement were significant risk factors for persistent vitamin D insufficiency, with adjusted odds ratio at 22.4 and 4.2 respectively (Table 2). No differences in gender and age at follow-up were found.

DISCUSSION

We reported the changes in serum 25OHD concentrations in a group of healthy infants with VDD in Hong Kong and identified the factors associated with persistent VDD. To our knowledge, no similar study had been conducted. Since VDD is prevalent in infants locally,[3] it is important to understand the natural history to plan for appropriate management. While the adverse impact of VDD on children's growth and skeletal development is well reported, VDD has also been shown in recent decade to be associated with overweight/obesity,[14,15] atopic dermatitis,[16] asthma,[17] impaired immunity with increased vulnerability to infections,[18] mental health problems[19] and various autoimmune diseases including type 1 diabetes and inflammatory bowel disease.[20] Therefore, it is particularly important to optimize the vitamin D status in infants and toddlers to avoid the occurrence of long-term health problems.

The usual recommended intake of vitamin D for healthy infants is 400 IU daily.[2,15] However, with ethnic and geographical variations, the daily intake recommendations for calcium or vitamin D vary considerably with different guidelines.[22] There were also studies showing that, despite daily supplementation of vitamin D 400 IU daily to newborns, vitamin D deficiency was still observed.[23–25] On the other hand, a treatment dose of vitamin D 2000 to 3000 IU daily would be needed for infants and toddler with VDD.[6] However, in clinical practice, recent measurement of serum 25OHD is often not available and the exact vitamin D status is often unknown. One im-

Table 2. Factors affecting the risk of persistent vitamin D insufficiency (25OHD <50 nmol/L)

	Crude association		Adjusted model	
	OR (95% CI)	*p*	a OR (95% CI)	*p*
Age (repeated age)	1.0 (1.0 – 1.0)	0.18	1.0 (1.0 – 1.0)	0.12
Gender				
Male	1.0		1.0	
Female	1.0 (0.5 – 2.3)	0.93	1.0 (0.3 – 2.8)	0.93
Exclusive BF	22 (8 – 61)	<0.0001	22 (4 – 118)	<0.001
Exclusive BF or formula <80%	13 (4 – 41)	<0.0001	-	
Formula ≥80%	0.07 (0.02 – 0.23)	<0.0001	0.5 (0.08 – 3.35)	0.49
No Vit D 400 IU supplementation	2 (0.7– 3)	0.4	4 (1 – 12)	0.01

BF: Breast feeding, OR: Odds ratio, 95% CI: 95% confidence interval

portant clinical question is whether blood test for 25OHD is needed for infants and to decide whether high dose vitamin D supplementation is needed. Our findings suggested that persistent VDD is uncommon among Hong Kong infants who were formula-fed or supplemented with vitamin D 400 IU daily for at least one month. However, for infants who were exclusive breastfed and not supplemented with vitamin D, in addition to clinical assessment for any sign of rickets, measurement of serum 25OHD might be necessary to decide if high dose vitamin D treatment is needed, as clinical signs of rickets might not be prominent and detectable in early phase, as illustrated in our cohort. Our findings were consistent with earlier studies to suggest that, with a low vitamin D concentration in breast milk, all breastfed infants should take 400 IU of vitamin D daily to prevent vitamin D deficiency.[10,26] This advice is further supported by the findings that show there is little risk of rickets in infants and children who consume one teaspoon of cod liver oil, which contains 400 IU of vitamin D per teaspoon. Nowadays, most parents in technologically-dependent societies rarely expose young infants to direct sunlight until well after 6 months, this prevents the natural synthesis of vitamin D using ultraviolet light.[27] Therefore, vitamin D supplementation in exclusively breastfed infants is essential.

On the other hand, upstream measures to prevent occurrence of VDD in newborns are also important. Since the fetal systemic vitamin D status is highly dependent on the maternal vitamin D concentrations, maternal vitamin D concentrations during pregnancy and vitamin D concentrations in cord blood are highly correlated.[28,29] Pregnancy is a period of tremendous growth and physiological changes for both the mother and her developing fetus, with long-term consequences for the child. Throughout pregnancy, adequate vitamin D substrate (via sunlight or supplement) is required to protect both mother and fetus, and when in sufficient supply, has a positive impact on the epigenome of the fetus, and thus long-term health.[27,30] Therefore, one important strategy to reduce VDD in newborns is to optimize the vitamin D status in pregnant women. Other than preventing VDD in newborns, in view of the potential effects of maternal vitamin D status on early placental development, angiogenesis and inflammation, it has been shown that vitamin D supplementation during pregnancy could reduce the risk of pre-eclampsia, gestational diabetes, low birthweight and may reduce the risk of severe postpartum haemorrhage.[31] Therefore, adequate prenatal vitamin D supplementation should be implemented in routine antenatal care to prevent pregnant ladies, and consequently, their newborns from having vitamin D deficiency. In addition, a prenatal vitamin D screening and treatment program can help detect deficient women, improve 25OHD concentrations, and reduce pregnancy-related complications.[32,33] Sufficient maternal vitamin D status was associated with substantial reduction in preterm birth risk in a large, diverse population of women.[34] Taken together, evidence suggests that vitamin D deficiency raises the risk of adverse pregnancy outcomes in both the mother and her developing fetus. For all these reasons, optimization of vitamin D status in pregnant women is crucial.

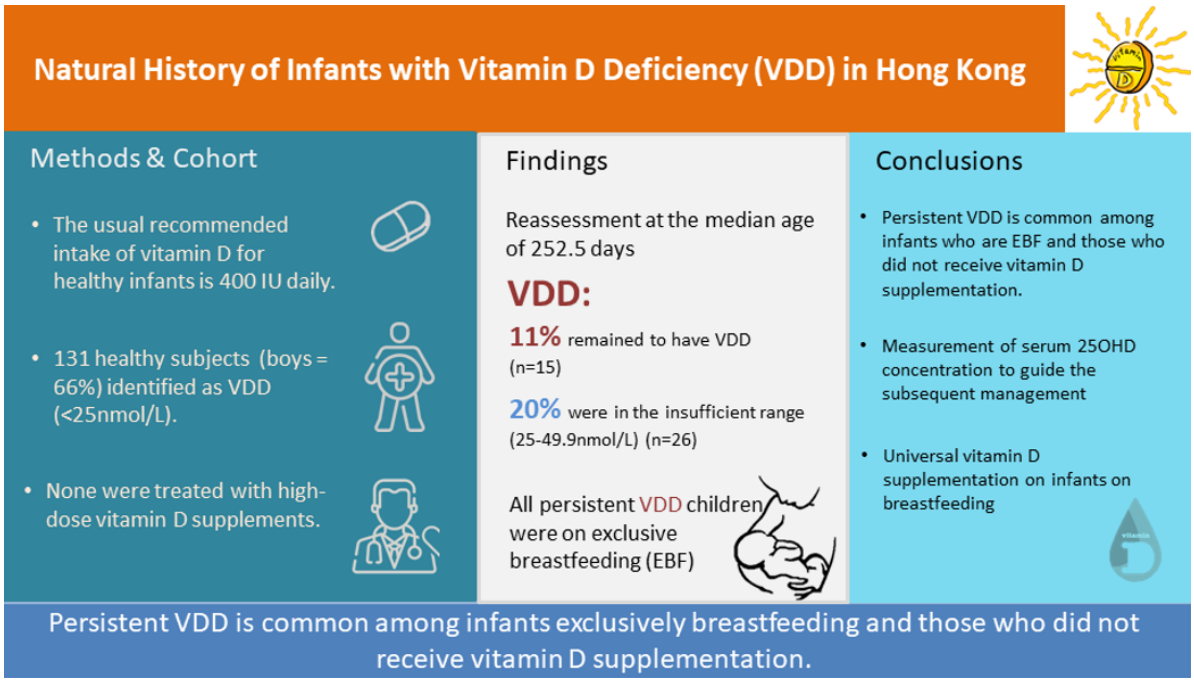
Findings of this study need to be interpreted with the following caveats. First, data on the infants' sun exposure, maternal vitamin D intake and maternal 25OHD concentration were lacking. All these factors may affect their 25OHD concentrations on follow-up. Second, the influences of genetic factors on vitamin D status have not been examined in this study. It has been shown in genome-wide association studies that, polymorphisms in genes functioning in vitamin D metabolism, e.g., vitamin D binding protein (GC), vitamin D receptor gene (VDR) and 24-hydroxylase (CYP24A1), are associated with serum 25(OH)D concentration.[35,36] Unfortunately, this data are not available in our cohort. However, such information is often difficult to ascertain in real-world clinical practice, and our findings helped to stratify the highest risk infants for serum 25OHD measurement to decide on whether high-dose vitamin D treatment is needed.

Policy recommendation

Based on the results we found, it is recommended to implement a policy of universal vitamin D supplementation for infants in Hong Kong. The following points support this recommendation:

1. Prevalence of VDD: VDD is prevalent among infants who are exclusively breastfed and those who did not receive vitamin D supplementation in Hong Kong. VDD has been associated with various long-term health problems, including growth and skeletal developmental issues, overweight/obesity, atopic dermatitis, asthma, impaired immunity, mental health problems, and autoimmune diseases. Optimizing vitamin D status in infants is crucial to prevent these health problems.

2. Recommended Intake: Based on our study, infants who have taken at least 1 month of vitamin D 400 IU daily were less likely to have persistent VDD. This sup-



Graphical abstract.

ports the usual recommendations of vitamin D 400 IU daily for healthy infants.

3. Serum 25OHD Measurement: Clinical assessment alone may not be sufficient to detect VDD in infants. For exclusively breastfed infants who are not supplemented with vitamin D, measurement of serum 25OHD should be considered to determine if high-dose vitamin D treatment is needed, as clinical signs of rickets may not be prominent in the early phase.

4. Breastfeeding and Sunlight Exposure: Breastfed infants are at a higher risk of VDD due to the low vitamin D concentration in breast milk. Additionally, in technologically-dependent societies like Hong Kong, infants are rarely exposed to direct sunlight until well after 6 months, further limiting the natural synthesis of vitamin D. Therefore, vitamin D supplementation is essential for exclusively breastfed infants.

5. Maternal Vitamin D Status: Maternal vitamin D concentrations during pregnancy have a significant impact on the fetal vitamin D status. Inadequate vitamin D intake of pregnant women can lead to VDD in newborns and increase the risk of pregnancy-related complications. Therefore, optimizing the vitamin D status in pregnant women through prenatal supplementation is crucial.

6. Benefits of Prenatal Supplementation: Adequate prenatal vitamin D supplementation not only prevents VDD in newborns but also reduces the risk of pre-eclampsia, gestational diabetes, low birthweight, and severe postpartum hemorrhage. It is also associated with a substantial reduction in preterm birth risk.

Conclusions

Persistent VDD is common among infants who are exclusively breastfed and those who did not receive vitamin D supplementation and hence measurement of serum 25OHD concentration should be considered to guide the subsequent management. On the other hand, VDD is common among infants in Hong Kong. Policy on universal vitamin D supplementation on infants on breastfeeding, starting shortly after birth, should be implemented to prevent VDD.

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AUTHOR DISCLOSURES

All authors have disclosed no conflicts of interest.

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