Eur J Nutr (2010) 49:395–400
DOI 10.1007/s00394-010-0097-8

ORIGINAL CONTRIBUTION

Is daily 400 IU of vitamin D supplementation appropriate for every country: a cross-sectional study

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Received: 10 September 2009 / Accepted: 1 February 2010 / Published online: 19 February 2010

Abstract

Background Vitamin D deficiency in childhood is a significant problem worldwide. Religious, social customs, and lack of food fortification were significant hurdles in the way of the rickets scourge. Recent data support a serum level of 25(OH)D level >40 ng/mL as the appropriate standard to achieve to prevent rickets. Herein, the current approaches of preventing rickets and optimal level of different vitamin D intakes were evaluated.

Methods A total of 148 fully breastfed, healthy children between age of 2–24 months were investigated by screening serum 25(OH)D from April 1 to May 31, 2006. Three groups were composed according to ages (2–6, 6–12, 12–24 months), and those groups were paired with three subgroups established according to vitamin D intake of $\leq$300, 400, and 600 IU/day. Vitamin D status was evaluated with regard to cut-off value of 15 ng/mL and 40 mg/dL. The clothing types and vitamin D supplementation of mothers were recorded.

Results We found that 27.3% of cases in 2–6 months, 8.3% in 6–12 months and 30% in 12–24 months had 25(OH)D <15 ng/mL and 54.5, 33.3, and 50% of cases were <40 ng/dL with 400 IU/day vitamin D intake. With 600 IU/day supplementation, 14.3, 10.3, and 4.8% of cases had 25(OH)D <15 ng/mL, respectively.

Conclusion Vitamin D intake of 400 IU/day seems to be favorable at the first year in breastfed children but vitamin D deficiency was still evident after prophylaxis. Vitamin D supplementation should be at least 600 IU/day in Turkey, and nutrition policy should focus on the food fortification with vitamin D.

Keywords Developing country · Vitamin D · Health Policy · Public Health · Infancy

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Introduction

New clinical researches over the past decades recommended daily intake of 200 IU vitamin D for all infants and children [1]. But, there is still challenging concern about current vitamin D supplementation regarding maternal vitamin D status during pregnancy, feeding types, food fortification and decreased sunlight exposure in infancy and childhood, age groups, environmental conditions and geographic locations, racial/ethnic groups.

Vitamin D deficiency continues to be a public health problem despite adequate sunlight exposure in many regions of Turkey [2, 3]. In 2005, the Ministry of Health in Turkey initiated a campaign nationwide for every infant to eradicate rickets with vitamin D supplementation of 400 IU/day [4]. Moreover, adequacy of the present vitamin

D daily supplementation is still being debated not only in Turkey but all over the world due to the multifactorial interference in establishing an optimal vitamin D status. A number of recent studies have highlighted that vitamin D deficiency is common during pregnancy as a consequence of social and religious customs in Turkey [5–9]. Additionally, it is believed that vitamin D supplementation in pregnancy and lactation should be increased over the recommended 400 IU/day [4, 10].

The latest reports seem to change our current understanding about vitamin D. It is well known that prolonged and severe vitamin D deficiency leads to rickets but its' effects on various organ systems and the cellular level are being discovered lately. Vitamin D should not be considered only in calcium and bone metabolism since it is accepted to be crucial in many chronic diseases [10, 11]. For that reason, rather than serum concentration at 15 ng/mL as a target of preventing clinical rickets, it should be considered to obtain optimal cut-off value of 40 ng/mL [12, 13].

Although nationwide campaign of the Ministry of Health has been carried out in our country, we observe different vitamin D intakes in childhood. In this study, we aimed to investigate the vitamin D status in 148 breastfed children between 2 and 24 months of age who were taking different doses of vitamin D daily supplementation ($\leq$300, 400 and 600 IU) and to compare these various approaches on the basis of preventing clinical rickets as vitamin D deficiency (cut-off value of 15 ng/mL) and optimal vitamin D levels as vitamin D insufficiency (cut-off value of 40 ng/mL).

Methods

A total of 148 healthy children between age of 2–24 months (9.4 $\pm$ 5.6 months) were evaluated by screening serum vitamin D concentrations in Ministry of Health Bakirkoy Maternity and Children Teaching Hospital from April 1 to May 31, 2006. The study population consisted of only fully breastfed children, and those received infant formula were excluded from the study. Three groups were designed according to ages (2–6, 6–12, 12–24 months). In each of age group, three subgroups were composed according to daily vitamin D intake of $\leq$300, 400, and 600 IU in the first year of life. All individuals received Devit-3 oral solution, Deva, Turkey (50,000 IU D3/15 mL) that contains 133 IU vitamin D3 in one drop. The cases got 1–3 drops ($\leq$300 IU), 3 drops (400 IU), and 5 drops (600 IU) per day. All data about vitamin D3 intakes were collected from mothers with face-to-face interview, and the used total box of Devit-3 oral solutions was noted. The cases with disorder usage of medication and individuals who had diagnosis of rickets or prematurity or any chronic diseases such as neurological, cardiac, renal, or hepatic disorders were excluded from our study. Anticonvulsant therapy was also an exclusion criterion. The study protocol was approved by the Ethics and Research Committee of the Ministry of Health Bakirkoy Maternity and Children Teaching Hospital.

The clothing types of mothers and vitamin D supplementation during pregnancy were recorded. It was shown that percentage of veiled mothers were high in all groups (<300, 400 and 600 IU) and showed statistical similarity (65–78%). Blood samples were taken for 25-hydroxyvitamin D [25(OH)D] from all the individuals. Samples were stored at −70 °C for 25(OH)D until analyzed and estimated by Biosource RIA kit International (Netherlands). The kit values for 25(OH)D ranged from 7.5 to 75 pg/mL. All cases were grouped with regard to cut-off value of 15 ng/mL as preventing level of clinical rickets and cut-off value of 40 ng/mL as optimal level of vitamin D. Vitamin D status were analyzed, and data were compared according to vitamin D intake in the same age group. Children in different age groups were also compared with regard to the similar vitamin D supplementation. We had also considered clothing habits (veiled or unveiled), ages of mothers, and vitamin D supplementation during pregnancy.

Statistical significance was assessed for discrete variable by χ^2 analysis and for continuous variables by t test or Kruskal–Wallis test, as appropriate. Qualitative variables were summarized as count and percentage. Medians were used to summarize quantitative data. Statistical significance was set at p-value < 0.05.

Results

Study group were composed of 148 fully breastfed children (70 men, 78 women). All cases received vitamin D supplementation regularly. The ages of mothers were between 19 and 39 years, mean 26.7 $\pm$ 4.6. The rate of vitamin D intake during pregnancy was 60.8%, and veiled clothing rate was 71. 6%. Mean duration of breast feeding was 7.3 months.

Cases were divided into 3 groups as 2–6 months ($n = 39$), 6–12 months ($n = 69$), 12–24 months ($n = 40$) according to their ages. Each of the groups was divided into three subgroups with regard to vitamin D intakes ($\leq$300, 400 and 600 IU).

Fourteen cases took $\leq$300 IU, 11 cases took 400 IU, and 14 cases took 600 IU vitamin D supplementation in 2–6 month-age group. There was no statistical difference between the subgroups about veiled clothing rate and vitamin D intake during pregnancy. Significant difference was noted about vitamin D insufficiency (<40 ng/mL); vitamin D status was under 40 ng/mL in all cases taking

≤300 IU, and 54.5% of cases taking 400 IU, and 42.9% of cases taking 600 IU (Table 1).

In 6–12 month-age group, 18 cases took ≤300 IU, 12 cases took 400 IU, and 39 cases took 600 IU vitamin D supplementation. There was no statistical difference between these subgroups about veiled clothing rate of mothers and vitamin D intake during pregnancy. Significant difference was noted about vitamin D insufficiency (<40 ng/mL). Vitamin D status was under 40 ng/mL in 77.8% of cases taking ≤300 IU, and 33.3% of cases taking 400 IU, and 17.9% of cases taking 600 IU (Table 2).

In 12–24 month-age group, 9 cases took ≤300 IU, 10 cases took 400 IU, and 21 cases took 600 IU vitamin D supplementation in the first year of life. We again figured out statistical difference about vitamin D insufficiency (<40 ng/mL) with similar veiled clothing rate and vitamin D intake rate during pregnancy in these subgroups. Vitamin D status was under 40 ng/mL in 88.9% of cases taking ≤300 IU, and 50% of cases taking 400 IU, and 9.5% of cases taking 600 IU (Table 3).

Furthermore, it was notable to see that 54.5% of cases in 2–6 months, 33.3% of cases in 6–12 months, and 50% of cases in 12–24 months suffered from vitamin D insufficiency (<40 ng/dL) who received recommended 400 IU vitamin D intake (Fig. 1).

When we considered the cut-off value of 15 ng/mL as vitamin D deficiency, we figured out that 27.3% of cases in 2–6 months, 8.3% in 6–12 months, and 30% in 12–24 months had vitamin D status under 15 ng/mL with 400 IU/day vitamin D supplementation (Table 4).

Table 1 Vitamin D insufficiency rates in 2–6 month-age group according to vitamin D supplementation

Vitamin D supplementation	≤300 IU/day	400 IU/day	600 IU/day	p*
2–6 months (n:39)				
25(OH)D level (median)	9.4 ng/mL	37.4 ng/mL	70.7 ng/mL	0.004
Vitamin D deficiency (<40 ng/mL)	n = 14/14	n = 6/11	n = 6/14	0.04
	100%	54.5%	42.9%	
Veiled clothing rate	71.4%	81.8%	71.4%	0.8
Age of mother	25.64 ± 4.6	26.82 ± 5.4	28.29 ± 4.7	0.37
Vitamin D intake in pregnancy	57.1%	63.6%	57.1%	0.93
Season	Spring (April 1st to May 31st)			

* p-values for comparing between three different vitamin D supplementation groups. Kruskal–Wallis test for continuous and count variables, Pearson X2 test for discrete variable

Table 2 Vitamin D insufficiency rates in 6–12 month-age group according to vitamin D supplementation

Vitamin D supplementation	≤300 IU/day	400 IU/day	600 IU/day	p*
6–12 months (n = 69)				
25(OH)D level (median)	9.5 ng/mL	77.6 ng/mL	70.2 ng/mL	0.02
Vitamin D deficiency (<40 ng/mL)	n = 14/18	n = 4/12	n = 7/39	0.00
	77.8%	33.3%	17.9%	
Veiled clothing rate	77.8%	66.6%	74.4%	0.79
Age of mother	24.72 ± 4.5	27 ± 5.6	27 ± 4.7	0.33
Vitamin D intake in pregnancy	50%	75%	64.1%	0.36
Season	Spring (April 1st to May 31st)			

*p-values for comparing between three different vitamin D supplementation groups. Kruskal–Wallis test for continuous and count variables, Pearson X2 test for discrete variable

Table 3 Vitamin D insufficiency rates in 12–24 month-age group according to vitamin D supplementation

Vitamin D supplementation	≤300 IU/day	400 IU/day	600 IU/day	p*
12–24 months (n = 40)				
25(OH)D level (median)	7.1 ng/mL	39.4 ng/mL	66.7 ng/mL	<0.001
Vitamin D deficiency (<40 ng/mL)	n = 8/9	n = 5/10	n = 2/21	<0.001
	88.9%	50%	9.5%	
Veiled clothing rate	66.7%	50%	71.4%	0.50
Age of mother	28.56 ± 4.4	27 ± 4.4	26.52 ± 3.5	0.41
Vitamin D intake in pregnancy	55.6%	60%	61.9%	0.94
Season	Spring (April 1 st to May 31st)			

*p-values for comparing between three different vitamin D supplementation groups. Kruskal–Wallis test for continuous and count variables, Pearson X2 test for discrete variable

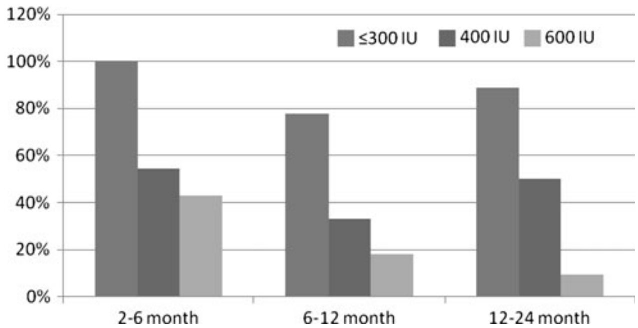

Fig. 1 Vitamin D insufficiency (<40 ng/mL) rates in three age groups in regard to the vitamin D intakes

Table 4 Cases with rickets level (25(OH)D ≤15 ng/mL) according to the age groups

	Vitamin D intake dose/day	25(OH)D ≤15 ng/mL (*n*)	25(OH)D ≤15 ng/mL (%)
2–6 month	≤300 IU	9/14	64.3
	400 IU	3/11	27.3
	600 IU	2/14	14.3
6–12 month	≤300 IU	12/18	66.7
	400 IU	1/12	8.3
	600 IU	4/39	10.3
12–24 month	≤300 IU	6/9	66.7
	400 IU	3/10	30
	600 IU	1/21	4.8

Discussion

In 1963, the American Academy of Pediatrics Committee on Nutrition recommended 400 IU of vitamin D per day for all infants and children. This recommendation was supported by the knowledge that 400 IU/day had been shown to prevent rickets. It was also observed that rickets could be successfully treated with 300–400 IU of vitamin D per day and a daily oral intake of 500 IU did not improve the response of rickets to vitamin D therapy [14]. After the late 1970s, this became an inconsistent recommendation, particularly for breast-feeding infants [15, 16]. In 2003, however, the American Academy of Pediatrics Committee on Nutrition recommended 200 IU/day vitamin D for all infants and children [17].

Despite widespread recognition, vitamin D deficiency is still prevalent in all over the world [18]. Persisting vitamin D deficiency may result from multifactorial interferences related to high growth rate and limited sunlight exposure in childhood, clothing habits of mothers and insufficient vitamin D intake during pregnancy and socioeconomic conditions of the countries. In fact, adequate sunlight exposure cannot be determined exactly for every subject. Also, there is an awareness of the hazards of ultraviolet-B light exposure in childhood and the subsequent development of skin cancer in adulthood. Lack of fortified supplements of vitamin D in developing countries and decreasing intake of vitamin D-fortified foods among older children address specific attention on this problem. In our study, we found that vitamin D deficiency (25(OH)D ≤15 ng/mL) was still evident between 12 and 24 months of age after prophylaxis, whereas vitamin D intake of 400 IU/day seems to decrease rickets rate at the first year of life (Table 4). It is obvious that a new definition of vitamin D supplementation should be optimized according to the population needs.

Critical question is 'which level should be obtained as optimal level of 25(OH)D in target of prophylaxis?' There is no absolute consensus as to what a normal range for 25(OH)D should be. Although vitamin D is essential for bone health, vitamin D deficiency is more than rickets. Actually, many types of cells in the body have vitamin D receptors, and vitamin D is functionally important in many other ways. Epithelial cells other than those of renal origin are capable of synthesizing 1,25-dihydroxyvitamin D from 25(OH)D [19, 20]. Vitamin D may also play a role in cancer prevention, so it appears to moderate colonic and prostate cell proliferation through vitamin D receptors [21, 22]. Approaches on the basis of preventing clinical rickets offer the cut-off value of 15 ng/mL, but this value is under the suppression level (20–30 mg/dL) of parathyroid hormone (PTH) [12, 13]. Chapuy et al. [23] reported that a dot plot of serum 25(OH)D levels as a function of PTH levels provided an insight about sufficient level of 25(OH)D. It is observed that the PTH levels began to plateau at their nadir when 25(OH)D levels were between 30 and 40 ng/mL [24–28]. Moreover, the level of 34 ng/mL is recommended for optimal calcium absorption [29]. In meta-analysis, it is announced that the risk of colon cancer decreased at 50% in serum concentration of 33 ng/mL and the rate of breast cancer incidence declined at 50% in serum concentration of 52 ng/mL of 25(OH)D [30, 31]. Unfortunately, there may be a serious misconception in the way of vitamin D deficiency due to the guidelines refer to prevent only particular metabolic bone diseases. Therefore, the authors believe that treatment should supply to maintain optimal level of which humans have naturally in a sun-rich environment, that is, >40 ng/mL, year around [13]. More researches are needed in pediatric population to determine the optimal dietary allowance of vitamin D. Eventually, the new data are needed to refine what constitutes vitamin D sufficiency or insufficiency.

In our study, if we consider the level of 25(OH)D <40 ng/mL as vitamin D insufficiency, we obtained vitamin D insufficiency in all the cases with ≤300 IU/day vitamin D intake and 50% of the cases with 400/600 IU/day vitamin D intake in 2–6 months group. Actually, vitamin D insufficiency rate was declined in 6–12 months group but unacceptable high rates of insufficiency persisted. Since reports have shown seasonal changes in plasma vitamin D levels in individuals, dependent on season-related sunshine duration per day, we conducted our study in a limited period in spring season to minimize the seasonal effect on vitamin D status. Definitely, it could not be ignored that vitamin D status had been worsen during winter time in our study, we found that vitamin D insufficiency apparently became a problem with $\leq$300 and 400 IU daily intakes after 12 months and only 600 IU/day vitamin D supplementation decreased the rate at 17.9–9.5% in the following months. Eventually, we thought that 600 IU intake might supply the optimal 25(OH)D status and protect from vitamin D insufficiency after prophylaxis ended in fully breastfed children in Turkey (Fig. 1).

In 2005, the Ministry of Health initiated a free vitamin D supplementation (400 IU/day) campaign nationwide for every infant to eradicate vitamin D deficiency or rickets in Turkey [4]. In fact, the prevalence of vitamin D deficiency associated with rickets decreased with the campaign, but rickets has been still a challenging childhood health problem in Turkey [32, 33]. We also noticed that rickets could not be eradicated with the current daily supplementation of 400 IU especially after 12 months of age. In our opinion, it is urgent that vitamin D supplementation should continue at least with food fortification beyond infancy in Turkey. Food fortification with vitamin D is essential in some countries as a nutrition policy. Foods that may be fortified with vitamin D include breakfast cereals, milk, milk products, grain products and pastas, infant formula, and margarine [34]. Particularly, recent amendments allow the addition of vitamin D to calcium-fortified juices and drinks [35]. More data are needed to support the adequacy of the present and possibly even higher vitamin D daily intakes.

Vitamin D deficiency is prevalent in early childhood in Turkey. We thought that vitamin D supplementation is crucial in developing countries since lack of food fortification with vitamin D and disadvantages of religious and social customs as veiled mothers. Especially, these factors affect children beyond the first year of life when prophylaxis was ended. In this study, we found that 400 IU of daily vitamin D intake was insufficient to obtain the optimal vitamin D status or even to prevent rickets in fully breastfed children in Turkey. Further studies are needed to evaluate this condition also in children that received infant formula. We suggest that vitamin D supplementation should be at least 600 IU/day in countries similar to our sociocultural conditions and food fortification with vitamin D should be encouraged in these countries.

Acknowledgments Not received any financial support.

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