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Factors affecting the vitamin D status in South Korean children

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Abstract: To establish the prevalence of vitamin D deficiency and insufficiency in healthy South Korean children aged between 1 month and 16 years and to identify factors affecting the serum vitamin D levels in South Korea. A total 969 healthy children were enrolled in this study. Serum levels of 25 hydroxyvitamin D (25(OH)D), calcium, phosphorous and alkaline phosphatase (ALP) were measured during a 1 year period. All the children were divided into four groups depending on the age. The prevalence of vitamin D deficiency (<15 ng/mL) was 20.5% and that of vitamin D insufficiency (15-20 ng/mL) was 19.5%. Overall, the mean serum 25(OH)D levels was 22.9±9.9 ng/mL. They were the highest in the preschoolers (2-5 years, 24.4 ng/mL) and the lowest in the adolescents (11-16 years,15.9 ng/mL). In addition, they were significantly higher in summer as compared with winter. There were eight cases of subclinical rickets with elevated serum ALP levels. The prevalence of vitamin D insufficiency and deficiency was relatively higher in our series of children. It is imperative that the public policies be established to provide vitamin D supplementation for South Korean children. In addition, pediatricians should consider such factors as the body mass index, sex, season and other risk factors when determining the optimal level of vitamin D.

Keywords: Vitamin D, Healthy Children, Risk Factor

1. Introduction

Vitamin D deficiency is an important public health problem in both developed and developing countries, with a reported worldwide prevalence of 30-80% in children and adults [1]. The role of vitamin D in bone mineralization has been well documented [2]. Moreover numerous studies have reported a link between vitamin D deficiency and several chronic disorders such as type 1 diabetes mellitus, systemic lupus erythematosus (SLE), multiple sclerosis (MS), cardiovascular disease (CVD) and several malignancies [3-5]. Based on these recent reports, there is a great emphasis on the importance of vitamin D supplementation in the treatment of patients with vitamin D deficiency.

25-hydroxyvitamin D (25[OH]D) is the major circulating form of vitamin D, whose serum levels are the best available indicator of total body vitamin D status [6]. That is, serum 25(OH)D levels are suggestive of vitamin D that was endogenously synthesized or obtained from the diet. Normal reference values for serum 25(OH)D levels depend on factors such as sunlight exposure, season, latitude, skin pigmentation, age, dietary vitamin D intake and assay method. There is still a debate on the definition of vitamin D deficiency and insufficiency in children. The 2011 Institute of Medicine (IOM) committee [7], in agreement with the Pediatric Endocrine Society [8], defined serum 25(OH)D levels of > 20 ng/mL (50 nmol/L) as the requirement in nearly all the children [9]. But, there is evidence that biochemical and skeletal sequelae of vitamin D deficiency may actually manifest at a higher cut-off level of 30-35 ng/mL [10]. Based on increased reports of vitamin D deficient rickets in young infants and toddlers, the American Academy of Pediatrics recommended that all breast-feeding infants be given vitamin D supplementation at a daily dose of 200 IU/day in 2003 [11] and it increased the daily dose to 400 IU/day in 2008 [8]. Nowadays, there is a tendency that children have limited sunlight exposure while spending more time indoors watching TV or doing computer things. This leads to the decreased vitamin D synthesis from the skin. Moreover, South Korea is a high-latitude country with four seasons.

Given the above background, we conducted this study to evaluate vitamin D status in healthy South Korean children and to identify its correlations with various factors. Our

results would contribute to preparing the healthcare policy for the prevention of vitamin D deficiency and the improvement of the vitamin D status in South Korea.

2. Method

2.1. Study Population

We studied healthy 969 children (n=969) aged between 0 and 16 years old who presented to the outpatient clinic for a routine check-up or vaccination. We excluded the children with rickets or hypocalcemia or those who had abnormal liver or renal functions that might affect hydroxylation of vitamin D, calcium and phosphorus metabolism. Then, we divided them into three groups according to serum 25(OH)D levels: the vitamin D deficiency group (serum 25(OH)D levels ≤ 15 ng/mL), the vitamin D insufficiency group (15 ng/mL < serum 25(OH)D levels < 20 ng/mL) and the vitamin D sufficiency group (serum 25(OH)D levels ≥ 20 ng/mL). In addition, we also classified them into four age groups depending on their age: the infants (1-12 months), the preschoolers (2-5 years), the middle children (6-10 years) and the adolescents (11-16 years). The current study was approved by the Institutional Review Board (IRB) of our medical institution. We obtained a written informed consent from the parents of children. The current study was conducted during a 1-year period ranging from January to December of 2012.

2.2. Serum Biochemistry

Blood sampling was done for serum biohemistry. Thus, we measured serum levels of calcium, phosphorus, alkaline phosphatase (ALP) and 25(OH)D. Serum 25(OH) D levels were quantified using chemiluminescent immunoassay. In addition, serum ALP levels were measured using colorimetric assay with a standardized method, where P-nitrophenyl phosphate and diethanolamine were served as a substrate and a buffer, respectively, for which we used Roche/Hitachi 917/MOD system. The intraassay coefficient of variation (CV) and the interassay one were 0.5% and 2.2%, respectively.

2.3. Statistical Analysis

Statistical analysis was done using the SPSS version 11.5 (SPSS Inc., Chicago, IL). All data was expressed as mean ± SD (SD: standard deviation) and the percentage (%). We compared measurements between the three groups using ANOVA, the t-test and the $\chi 2$ test. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Baseline Characteristics

Baseline characteristics of the children are summarized in Table 1. We enrolled a total 975 children with a mean age of 4.07± 3.39 years old (range, 1-6 years old). Serum 25(OH)D levels were measured from 969 children. They consisted of 547 boys (56.4%) and 422 girls (43.6%).

Table 1. *Characteristics of study participants*

Characteristic	n(%)
Sex	
Male	745(56.4)
Female	422(43.6)
Age	
1-12 months	187 (19.3)
2-5 years	532 (54.9)
6-10 years	125 (12.9)
11-16 years	125 (12.9)
Weight	
Normal weight	545(56.2)
Under weight (< 5th percentile)	140 (14.4)
Over weight (85th to <95th percentile)	187 (19.3)
Obesity (≥95th percentile)	97 (10)
Season of data collection	
March to May	233(24.0)
June to August	235 (24.3)
September to November	322 (33.2)
December to February	179 (18.5)
Vitamin D status (serum 25[OH]D concentration [ng/mL])	
Deficient (<15ng/ml)	197 (20.5)
Insufficient (15ng/ml to <20ng/ml)	188 (19.5)
Sufficient (≥20ng/ml)	584 (60.0)

By the weight, based on the body mass index (BMI) that was available for more than two years, we classified the children into four groups: the underweight group (n=140, 14.4%), the normal weight group (n=545, 56.2%), the overweight group (n=187, 19.3%) and the obese group (n=97, 10%). Overall, the mean serum 25(OH) D level was 22.9±9.9 ng/mL. Of the 975 children, 40% had abnormal serum 25(OH) D levels. Moreover, 197 (20.5%) and 188 children (19.5%) were classified into the vitamin D deficiency group and the vitamin D insufficiency group, respectively. The mean serum 25(OH) D levels were slightly lower in girls than boys (22.6 ng/mL vs. 23.3 ng/mL, P=0.156).

3.2. Correlations between Serum 25(OH) D Levels and the Age

In all the age groups except for the infants, the mean serum 25(OH)D levels were decreased as the age was increased. But they were lower in the infants as compared with the preschoolers. Moreover, they reached the highest level (24.4 ng/mL) in the preschoolers. In addition, there were significant differences in them between the middle children (20.5 ng/mL) and adolescents (15.9 ng/mL). There were no significant differences in mean serum 25 (OH) D levels between boys and girls with no respect to the age. But the mean serum 25(OH) D levels were lower in the adolescent girls as compared with the adolescent boys (P=0.05) (Figure 1). The correlation between the vitamin D status based on the mean serum 25(OH) D levels and the age is shown in Figure 2. Furthermore, correlations between the anthropometric and metabolic characteristics and the vitamin D status are given in Table 2. The mean BMI was

significantly higher in the vitamin D deficiency group as compared with the vitamin D sufficiency group.

Table 2. *The anthropometrics and metabolic characteristics of the study population*

Variable	Vitamin D status			
	Deficiency	Insufficiency	Sufficiency	P-value
Age, years	4.42 ± 3.62	4.47 ± 3.72	2.61 ± 2.43	<0.001
Female (%)	40.4	48.4	43.1	0.52
BMI (kg/m^2)	17.89 ± 5.43	17.02 ± 4.3	16.12 ± 2.02	0.001
25(OH)D (ng/mL)	10.05 ± 3.50	17.70 ± 1.40	28.91 ± 7.57	<0.001
Ca (mg/dL)	9.95 ± 0.57	9.76 ± 0.45	9.71 ± 0.75	0.86
P (mg/dL)	4.99 ± 0.69	4.92 ± 0.54	5.48 ± 0.71	0.28
ALP(U/L)	653 ± 270	578 ± 174	512 ± 339	0.049

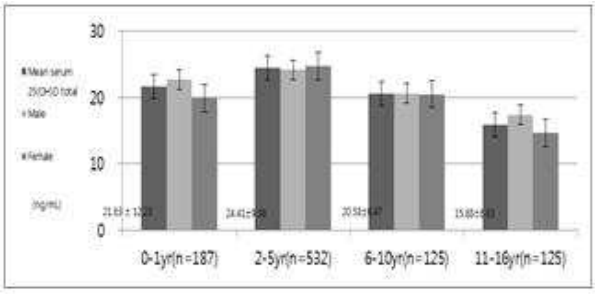

Figure 1. *Mean serum 25(OH)D levels by the different age and sex groups. yr:Years*

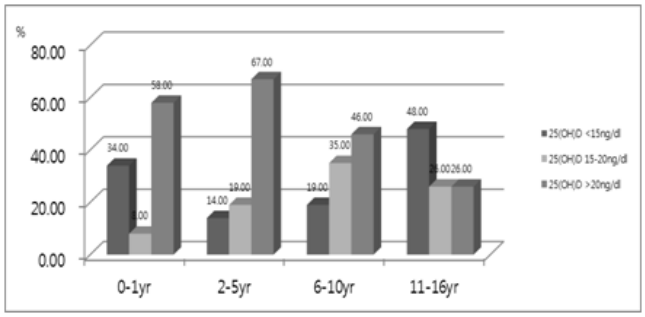

Figure 2. *The prevalence of each category of vitamin D status by the different age group. Yr:Years*

Overall, the mean serum levels of calcium, phosphorus and ALP were 9.8±1.12 mg/L, 5.13±0.81 mg/L and 581±70.5 U/L, respectively. There were no significant differences in mean serum levels of calcium and phosphorus between the three groups. In addition, serum ALP levels were significantly higher in the vitamin D deficiency group as compared with the vitamin D sufficiency group.

3.3. Correlations between Serum 25(OH) D Levels and the Season

Mean serum 25(OH) D levels by month are shown in Figure 3. They were the highest in August and the lowest in December and February. Twelve months were divided into four seasons (Spring – March, April and May; Summer – June, July and August; Autumn – September, October and November; and Winter – December, January and February). There was a change in the mean serum 25(OH) D levels depending on the season. In all the age groups except for the infants, they were gradually increased in the order of Winter, Spring or Autumn and Summer. In the infants, mean serum 25(OH) D levels were significantly higher in Winter as compared with Spring and Summer (Figure 4).

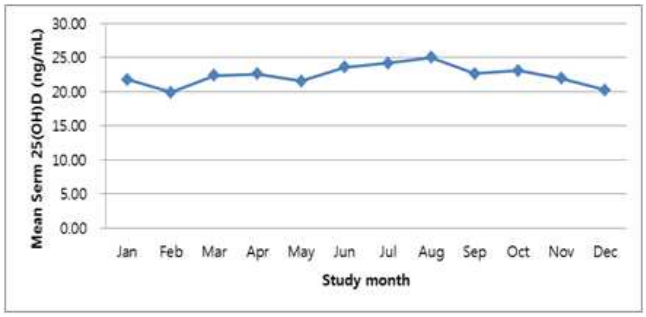

Figure 3. *Mean serum 25(OH)D levels by month.*

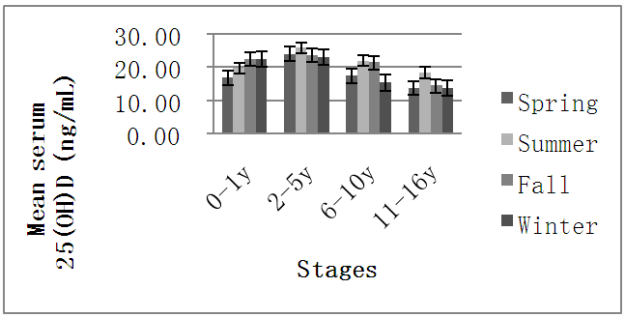

Figure 4. *Mean serum 25(OH)D levels by the different age and sex groups. y:Years*

3.4. Subclinical Rickets

In the current study, we reviewed radiographs of the children to identify rickets in 191 children with serum 25(OH)D levels of < 10 ng/mL (n=80) and those with serum ALP levels of > 800 IU (n=126). This revealed the presence of subclinical rickets in eight children.

Serum ALP levels were elevated in all the children, but there was a variability in serum 25(OH)D levels (Table 3).

Table 3. *Profiles of Subclinical Rickets patients*

Patient No.	Sex	Age (month)	Month at Diagnosis	serum 25 (OH) D (ng/mL)	ALP (U/L)	Ca (mg/dL)	P (mg/dL)
1	M	4	March	<4	1018	10.1	4.4
2	M	13	November	<4	2231	9.2	5.6
3	M	4	April	<4	1448	10.5	2.6
4	F	5	September	7.7	941	10.4	5.5
5	M	5	March	10.1	927	10.7	3.6
6	F	4	January	22.4	823	9.5	4.5
7	F	14	November	28.3	1747	9.4	4
8	M	12	January	35.4	1063	10.1	5.3

4. Discussion

The current study first attempted to determine the vitamin D status in a large series of healthy South Korean children. Our results showed that 386 children (40%) had a vitamin D

insufficiency and this is a relatively higher value. Moreover, our results also showed that197 children (20.5%) had a vitamin D deficiency and this is relatively higher as compared with other countries. Our data showed that the mean serum 25(OH)D levels in the infants were significantly lower as compared with other reports. This is mainly because there are no formal recommendations about vitamin D supplementation for infants in South Korea unlike other countries. In many countries including the US, however, all the children are recommended to take vitamin D at a daily dose of 400 IU/day after birth [12-14]. In South Korea, breast milk or formula one are often mistakenly considered perfect nutrients for baby. This leads to lack of supply of other nutrients for their baby. Furthermore, families and physicians tend to use multivitamins or other nutrients more frequently after 12 months postnatally. In the current study, the proportion of children with serum vitamin D levels of < 20 ng/mL in most of the age groups was significantly higher as compared with the US reports; it was 33% vs. 14% in the preschoolers, 53% vs. 20% in the middle children and 74% vs. 28.8% in adolescents. We conducted the current study in a city with latitude 37° N. As compared with other studies that had been conducted in the areas with the same latitude, including Turkey [15], our results showed that the mean serum 25(OH)D levels were significantly lower in the two age groups; it was 34.2 ng/mL vs. 24.4 ng/mL in the preschoolers, 20.5 ng/mL vs. 20.5 ng/mL in the middle children 18.7 ng/mL vs. 15.8 ng/mL in the adolescents. It is therefore imperative that a vitamin D prophylaxis augmentation programme be prepared in South Korean children. Given the concerns for vitamin D deficiency in older children and adolescents, the American Academy of Pediatrics released a new recommendation that all the children receive vitamin D at a daily dose of 400 IU/day from the birth to the adolescence [11]. Here, we therefore propose a recommendation on vitamin D supplementation for South Korean children – from infants to adolescents. It has also been reported that the vitamin D insufficiency was more prevalent in adolescent girls as compared with boys in the US [16]. Our results showed that the vitamin D deficiency was more prevalent in girls, adolescent girls in particular, as compared with boys with no respect to the age for unknown reasons. In Muslim countries, adolescent girls constitute a risk group of developing vitamin D deficiency because they wear a traditional covered dress [17, 18]. Consistent with other reports, our results also showed that there was a negative correlation between serum vitamin D levels and the BMI [19, 20]. According to adult studies, the vitamin D insufficiency was more prevalent in overweight or obese people [21].

Presumably, a negative correlation between the two factors might be explained based on the findings that the vitamin D is sequestered in the subcutaneous body fat and this eventually reduces its bioavailability [22]. Moreover, it has also been reported that fewer outdoor activities and reduced sunlight exposure in obese people individuals are also responsible for the reduced endogenous vitamin D synthesis [23].

Our results showed that the mean serum 25(OH)D levels in the children aged between 2 and 16 years varied depending on the season. That is, they were very low in winter, were slightly higher in spring and reached the highest in summer. Their variability depending on the season was more notable in the adolescents. Presumably, this might be because children are commonly dressed in multi-layered outfits when going outdoors in winter with less sunlight exposure [24]. Moreover, many South Korean adolescents have limited sunlight exposure not only because they spend more time indoors doing computer things but also because there are insufficient playgrounds. In association with this, it has been reported that overweight children are at increased risks of developing vitamin D insufficiency with a poorer vitamin D status if they exercise outdoors for less than half an hour per day and week and watch TV for more than 2.5 hours per day and week. This suggests that the degree of sunlight exposure is a potentially modifiable risk factor [25]. This explains why South Korean children should be given the increased opportunity to get safe sunlight exposure and they are encouraged to do more outdoor activities in winter season in particular.

Our results showed that the mean serum 25(OH)D levels in the children aged between 1 and 12 months were highest in winter, but there were no significant differences in them between the seasons. The major source of circulating 25(OH)D concentration in young infants is their mother, so the maternal vitamin D status in an important factor in determining the vitamin D status of the infants, breast-feeding infants in particular [26]. To date, few studies have reported the prevalence of hypovitaminosis D during pregnancy [27]. Based on our reports, we suggest that more effective vitamin D prophylaxis programs should be implemented in pregnant women as well as their babies.

The mean serum levels of calcium and phosphorus were within normal values in our study. There were no significant differences in them between the vitamin D deficiency group and the vitamin D sufficiency group. Moreover, our results also showed that the mean serum ALP levels were significantly higher as compared with other reports [28]. This is because we enrolled a large number of infants in the current study. It has been reported that the mean serum ALP levels reach the highest value during the rapid growth phase of childhood such as infancy and puberty [29]. Our results showed that there were significant differences in the mean serum ALP levels between the vitamin D deficiency group and the vitamin D sufficiency group ($P<0.05$). According to some reports, the mean serum ALP levels might be a good indicator in screening breast-feeding children who are predisposed to rickets [28, 30]. In our study, the mean serum ALP levels were significantly higher in all the children with subclinical rickets. Taken together, our results suggest that the mean serum ALP levels may be a better indicator of functional vitamin D status and it is useful to screen healthy infants and toddlers who are predisposed to rickets.

5. Conclusions

Our results showed that vitamin D deficiency and insufficiency were highly prevalent in South Korean children with no respect to the age.

Based on our results, we can conclude the following:

(1) It is imperative that public health strategies be prepared to provide all infants with vitamin D supplementation at a daily dose of 400 IU/day immediately after birth. Moreover, children are at increased risks of developing suboptimal vitamin D depending on the age. They should therefore be given vitamin D supplementation at a dose of IU/kg.

(2) It is necessary to for children use dairy products containing vitamin D supplements. This is essential for preventing vitamin D deficiency.

(3) The importance of outdoor activities and safe sunlight exposure should be promoted through public health messages and interventions.

(4) Pediatricians are committed to actively promoting bone health by encouraging children to take adequate vitamin D.

Further nationwide studies are warranted to increase the awareness of the importance of vitamin D supplementation in the prevention of vitamin D deficiency.

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