Research Article

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Determination of vitamin 25-hydroxyvitamin D deficiency and insufficiency cut-off values in children

Çocuklarda 25-hidroksivitamin D eksiklik ve yetersizlik sınır değerlerinin araştırılması

Abstract

Objectives: There is no consensus on the lower and upper limits of 25-hydroxyvitamin D (25-OHD) deficiency and insufficiency. We determined the (25-OHD) deficiency and insufficiency cut-off values in children.

Methods: The study examined 422 children aged 0–18 years old whose simultaneous parathormone (PTH) and (25-OHD) levels were measured at the paediatric outpatient clinics of our tertiary research hospital in Istanbul from January 1, 2014 to December 31, 2017. Those without chronic diseases were included in this cross-sectional retrospective study.

Results: We found that the average serum (25-OHD) level was lower in girls. There were negative correlations between (25-OHD) and PTH and age. The level that decreased PTH below the upper level was 14.42 ng/mL and the 25(OH) D level that decreased it to the lowest limit was 26.61 ng/mL. The (25-OHD) level that caused maximum suppression of PTH was 22.5 ng/mL.

Conclusions: The vitamin (25-OHD) deficiency (lowest value) and insufficiency (range) cut-off should be 14–23 ng/mL for children living in Istanbul. By age subgroup, the vitamin (25-OHD) deficiency and insufficiency cut-off values are 21–31, 15–21 and 13–18 ng/mL for those 0–2, 3–6 and 7–18 years, respectively.

Keywords: children; cut-off value; deficiency; parathormone; vitamin D.

Özet

Giriş: 25 hidroksivitamin D (25-OHD) eksikliği ve yetersizliğinin alt ve üst sınırları konusunda fikir birliği yoktur. Biz de çocuklarda, (25-OHD)' nin eksiklik ve yetersizlik sınır değerlerini araştırdık.

Gereç ve Yöntem: Çalışma, 1 Ocak 2014 ile 31 Aralık 2017 tarihleri arasında, İstanbul' daki 3. basamak hastanemizin çocuk polikliniğine başvuran ve aynı anda Parathormon ve (25-OHD); bakılan, 0–18 yaş arası 422 çocuk ile gerçekleştirildi. Geriye dönük kesitsel çalışmamıza, kronik hastalığı olanlar dahil edilmedi.

Bulgular: Ortalama serum (25-OHD) düzeyini kızlarda daha düşük bulduk. (25-OHD) ile Parathormon ve yaş arasında negatif ilişki vardı. Parathormonunu, normal değerlerinin üst sınırının altına inmesini sağlayan (25-OHD) düzeyi 14.42 ng/mL ve alt sınırının altına inmesini sağlayan (25-OHD) düzeyi 26.61 ng/mL dir.Parathormonun en çok baskılanmasına neden olan (25-OHD) düzeyi 22.5 ng/mL dir.

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Sonuç: İstanbul' da yaşayan çocuklar için, (25-OHD) eksiklik alt sınırı ve yetersizlik aralığı 14–23 ng/ml olmalıdır. Yaş gruplarına göre (25-OHD) eksiklik ve yetersizlik sınır değerleri 0–2, 3–6 ve 7–18 yaşlar için sırasıyla; 21–31, 15–21 ve 13–18 ng/mL dir.

Introduction

25-hydroxyvitamin D (25-OHD) has a primary role in ensuring calcium and phosphorus absorption from the intestines. The prevention and treatment of (25-OHD) deficiency are essential for preserving and sustaining bone health. (25-OHD) deficiency or insufficiency is still a major public health issue in Turkey, although there is sufficient sunlight [1]. A recent study of (25-OHD) deficiency in Turkish children reported that the rates of vitamin D insufficiency and deficiency were 51.5 and 35.1%, respectively [2]. However, there is no consensus on the lower and upper laboratory values of (25-OHD) deficiency and insufficiency. In 2008, the American Academy of Pediatrics accepted ≤25-OHD 15 ng/mL as indicating (25-OHD) deficiency and the range 15–20 ng/mL as indicating insufficiency in children [3]. The most recent global consensus report proposed 25-OHD 12 ng/mL as the limit for (25-OHD) deficiency and 12–20 ng/mL the range for insufficiency [4]. This may depend on other laboratory parameters, such as serum parathormone (PTH) levels, which are influenced by the change in (25-OHD) levels as much as by the method used to measure serum 25-OHD levels in the laboratory.

Among vitamin D forms, serum 25-OHD has the longest half-life and is commonly measured since the half-life of active vitamin D is short. It is usually not used, except in cases of vitamin-D-resistant rickets. Moreover, optimal vitamin D levels are closely related to the serum PTH level. Vitamin D controls the serum PTH level together with calcium. In this way, optimal serum vitamin D can maintain serum PTH levels within optimal limits.

This study examined the cut-off values of (25-OHD) deficiency and insufficiency in children aged 0–18 years living in Istanbul, Turkey, by evaluating serum 25-OHD and PTH levels.

Materials and methods

This cross-sectional study was approved by our hospital ethics committee (approval no. 583, date 21.1.2017). The study enrolled 422 children aged 0–18 years with no chronic diseases who visited the paediatric outpatient clinics of our tertiary research hospital in Istanbul between January 1, 2014 and December 31, 2017. During this period, (25-OHD) and PTH were determined in 748 patients. The subjects' clinical and sociodemographic details and laboratory values were acquired from the hospital information management system. Because both tests were not ordered concurrently, 295 patients were excluded, as were 13 patients with parathyroid or bone tumours, 11 with vitamin D-induced intoxication and seven with bone metabolism disorders. Ultimately, the study included 422 children with both serum 25-OHD and PTH levels. The subjects were subdivided into prepubertal and adolescent groups.

The serum total (25-OHD) and PTH levels were quantified using chemiluminescence immunoassays on the UniCel Dxl 800 analyser (Beckman Coulter, USA). (25-OHD) showed clinically acceptable linearity over the analytical measurement range of 2.00–210 ng/mL. The within and between coefficients of variance of the (25-OHD) measurements were 3.5 and 6.3%, respectively, and those for PTH were 2.1 and 3.9%. The lowest detectable PTH level that could be distinguished from zero with a 95% confidence level was 1 pg/mL.

Statistical analysis

SPSS 15.0 for Windows was used for statistical analyses. Descriptive statistics were provided as the average, standard deviation and range for quantitative variables and number and percentage for categorical variables. When the distribution of quantitative variables was not normal using the Kolmogorov–Smirnov test, the Mann–Whitney U-test was used to compare two independent groups and the Kruskal–Wallis test to compare more than two groups. Subgroup analyses were performed with the Mann–Whitney U-test with the Bonferroni correction. Relationships between non-parametric variables were analysed using Spearman correlation analysis. Section values were analysed using receiver operating characteristic (ROC) curve analysis. Values that cause maximal suppression were determined with the curve estimation test. The statistical level of significance was accepted as p<0.05.

Results

The mean age of the 422 subjects was 6.6 ± 5.9 (0–17) years; 213 (50.5%) were male and 209 (49.5%) were female. Table 1

Table 1: Age, gender, puberty conditions of patients and distribution of laboratory tests.

Age, year (mean ± SD [min−max])	6.6 ± 5.9 (0−17)
Gender (n, %)	
Male	213 (50.5)
Female	209 (49.5)
Puberty (n, %)	
Adolescent	299 (70.8)
Prepuberty	123 (29.2)
Calcium, mg/dL (mean ± SD [min−max])	10.0 ± 0.5 (7.9−12.1)
Phosphorus, mg/dL (mean ± SD [min−max])	4.9 ± 0.8 (2.6−7.24)
Alkaline phosphatase, IU/L (mean ± SD [min−max])	298.1 ± 421.7 (53.5−5253.1)
(25-OHD), ng/mL (mean ± SD [min−max])	22.6 ± 12.7 (3.54−75.1)
Parathormone, pg/mL (mean ± SD [min−max])	40.5 ± 24.4 (10.4−150,1)

25-OHD, 25-hydroxyvitamin D.

Table 2: 25-hydroxyvitamin D (25-OHD), parathormone and age correlation.

	Parathormone (pg/mL)		(25-OHD) (ng/mL)	
	ρ	p-Value	ρ	p-Value
(25-OHD) (ng/mL)	−0.508	<0.001	–	–
Age	0.254	<0.001	−0.447	<0.001

Table 3: Parathormone and 25-hydroxyvitamin D (25-OHD) differences in gender, season and puberty condition.

n	Parathormone (pg/mL)		(25-OHD) (ng/mL)	
	Mean ± SD	Median	Mean ± SD	Median
Gender				
Male (213)	39.2 ± 20.4	32.6	24.5 ± 13.4	21.7
Female (209)	42.3 ± 29.3	35.8	20.6 ± 11.7	17.9
p		0.362		0.002
Seasons				
Spring (101)	41.6 ± 23.5	35.7	19.4 ± 11.8	15.9
Summer (82)	41.0 ± 31.9	35.1	26.8 ± 13.3	23.48
Autumn (112)	37.2 ± 22.1	32	22.5 ± 9.4	21.1
Winter (117)	44.6 ± 26.3	38	21.5 ± 14.4	17.4
p		0.129		<0.001
Puberty (%)				
Adolescent (299)	36.6 ± 21.5	30.52	25.0 ± 13.2	22.395
Prepubertal (123)	48.2 ± 27.5	41.5	16.5 ± 8.7	14.4
p		<0.001		<0.001

Table 4: 25-hydroxyvitamin D (25-OHD) values which correspond to ROC curve and various values of parathormone.

Parathormone (pg/mL)	Number of patients and ratio	(25-OHD) (ng/mL)	ROC % sensitivity–specificity
<12	4–0.9%	26.61	0.750–0.699
<15	4.3–18%	26.17	0.889–0.714
<20	58–13.7%	24.72	0.724–0.721
<35	207–48.9%	20.14	0.700–0.704
<65	374–88.4%	14.42	0.733–0.735
<88	403–95.3%	11.34	0.841–0.800

Table 5: 25-hydroxyvitamin D (25-OHD) value, which realizes parathormone (PTH) maximal suppression.

	Mean	Median	%95 CI	
			Min	Max
(25-OHD) (ng/mL) value with maximal PTH suppression, LINEAR	22.51	23.76	21.99	23.02
(25-OHD) (ng/mL) value with maximal PTH suppression, QUADRATIC	22.51	23.12	21.95	23.07

CI, confident interval.

summarizes their clinical and laboratory values. There was no significant (p>0.05) difference between the subjects by gender. PTH was significantly (p<0.001) negatively correlated with (25-OHD) and positively correlated with age (25-OHD) was significantly (p<0.001) negatively correlated with age (Table 2).

The (25-OHD) level was significantly (p=0.002) higher in males than in females. The PTH level of adolescents was significantly lower than in prepubertal subjects, while the (25-OHD) level was significantly higher (both p<0.001). The (25-OHD) levels were highest in summer and lowest in the spring (Table 3).

Table 4 shows the study results of the interaction of (25-OHD) with PTH levels. Using ROC curve analysis, the (25-OHD) level that realized maximal suppression of PTH was 22.5 ng/mL (Table 5; Figure 1).

Table 6 presents the PTH and (25-OHD) values for different age groups, while Table 7 shows the interaction of (25-OHD) with PTH levels and the ROC curve according to age groups. Using the curve estimation method, the (25-OHD) that realized maximal suppression of PTH was 31.20, 20.44 and 17.07 ng/mL for the 0–2, 3–6 and 7–18 year age groups, respectively (Table 8; Figures 2–4).
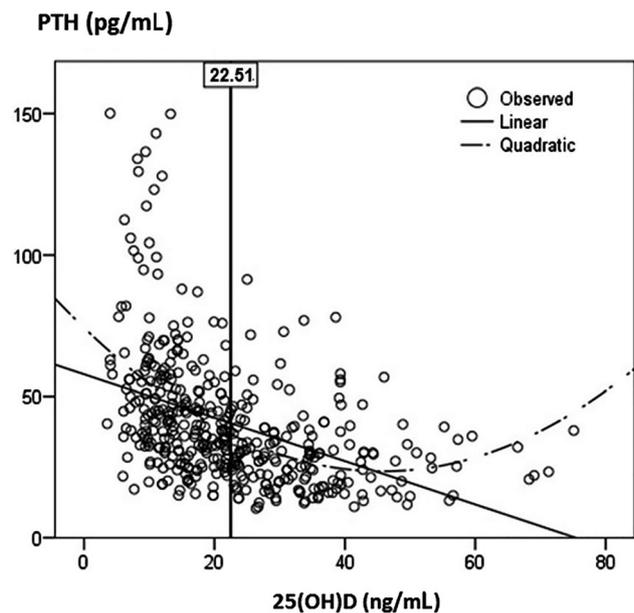

Figure 1: Graphical representation of vitamin 25(OH)D level which demonstrates maximal suppression of parathormone (PTH) for 0–18 age group.

Table 6: Parathormone and 25-hydroxyvitamin D (25-OHD) values according to subgroups.

Year	Parathormone (pg/mL)			(25-OHD) (ng/mL)		
	Mean	**Min–Max**	**Median**	**Mean**	**Min–Max**	**Median**
0–2	34.5 ± 20.7	10.4–143	29.8	31.2 ± 14.4	4.1–75.1	30.01
3–6	40.2 ± 23.1	12.3–129.5	35.6	20.4 ± 10.1	6.1–66.5	19.9
7–18	45.0 ± 24.0	12.4–150.1	41	17.5 ± 9	3.5–47.8	15.4
p			<0.001			<0.001

Table 7: 25-hydroxyvitamin D (25-OHD) values which correspond to ROC curve and various values of parathormone (PTH) according to subgroups.

PTH (pg/mL)	Year	n	AUC	AUC	%95 CI	Cut-off (25-OHD) (ng/mL)	Sensitivity (%)	Specificity (%)
PTH <12	0–2	4	0.627	0.408	0.846	30.0	50.0	50.0
	3–6	0	–	–	–	–	–	–
	7–18	0	–	–	–	–	–	–
PTH <15	0–2	8	0.738	0.593	0.884	35.02	75.0	66.7
	3–6	6	0.857	0.752	0.961	23.20	100	70.8
	7–18	4	0.917	0.872	0.962	26.19	100	87.8
PTH <20	0–2	28	0.704	0.617	0.792	35.02	67.9	72.6
	3–6	11	0.716	0.557	0.876	23.20	72.7	71.4
	7–18	19	0.735	0.614	0.856	19.75	68.4	70.1
PTH <35	0–2	90	0.727	0.628	0.825	26.16	74.4	68.2
	3–6	47	0.774	0.680	0.868	19.58	76.6	72.9
	7–18	70	0.708	0.634	0.782	15.94	68.6	67.5
PTH <65	0–2	124	0.819	0.679	0.958	21.39	79.0	80.0
	3–6	84	0.801	0.694	0.907	15.33	71.4	81.8
	7–18	166	0.707	0.598	0.815	13.34	65.1	59.3
PTH <88	0–2	131	0.967	0.933	1.001	11.25	95.4	100
	3–6	90	0.881	0.789	0.973	12.15	78.9	100
	7–18	182	0.769	0.628	0.910	10.81	81.3	72.7

Table 8: 25-hydroxyvitamin D (25-OHD) value, which realizes parathormone (PTH) maximal suppression according to subgroups.

	Mean	**Median**	**Min[a]**	**Max[a]**
(25-OHD) (ng/mL)				
0–2 years				
(25-OHD) value with maximal PTH suppression, linear	31.20	30.15	32.25	32.59
(25-OHD) value with maximal PTH suppression, quadratic	31.20	30.11	32.29	32.27
3–6 years				
(25-OHD) value with maximal PTH suppression, linear	20.44	19.46	21.42	21.39
(25-OHD) value with maximal PTH suppression, quadratic	20.44	19.37	21.51	20.63
7–18 years				
(25-OHD) value with maximal PTH suppression, linear	17.07	17.07	17.92	17.99
(25-OHD) value with maximal PTH suppression, quadratic	17.07	17.04	17.94	17.62

[a]Confident interval.

Discussion

The mean overall (25-OHD) level was 22.6 ng/mL and that of PTH was 40.5 pg/mL. The mean age of the group was 6.6 (0–17) years and there was no significant (p>0.05) difference between females and males (Table 1). We found a negative correlation between the PTH and (25-OHD) levels, as expected ($\rho=-0.508$, p<0.001). There was also a negative correlation between (25-OHD) and subject age ($\rho=-0.447$, p<0.001) (Table 2). However, the mean (25-OHD) level of adolescents subjects was significantly (p<0.001) higher than that of prepubertal subjects (Table 3).The literature reports that serum 25-OHD values decrease with increasing age, particularly during puberty, since the demand is increased with the accelerated bone formation [5, 6]. Our outcome may have resulted because there were more prepubertal patients and because of the seasonal effects of calcium intake and nutritional conditions. Because of its
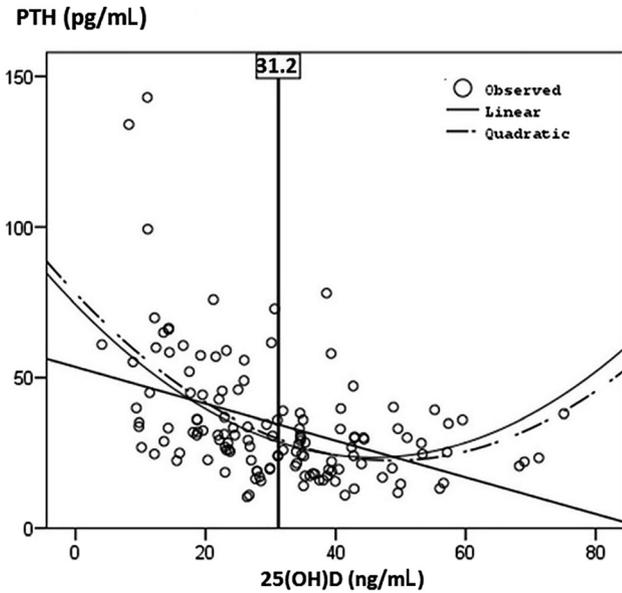
Figure 2: Graphical representation of vitamin 25(OH)D level which demonstrates maximal suppression of parathormone (PTH) for 0–2 age group.
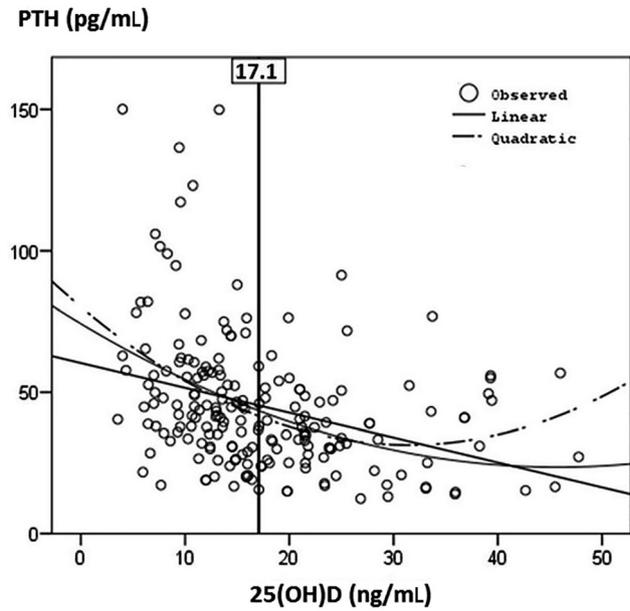

Figure 4: Graphical representation of vitamin 25(OH)D level which demonstrates maximal suppression of parathormone (PTH) for 7–18 age group.
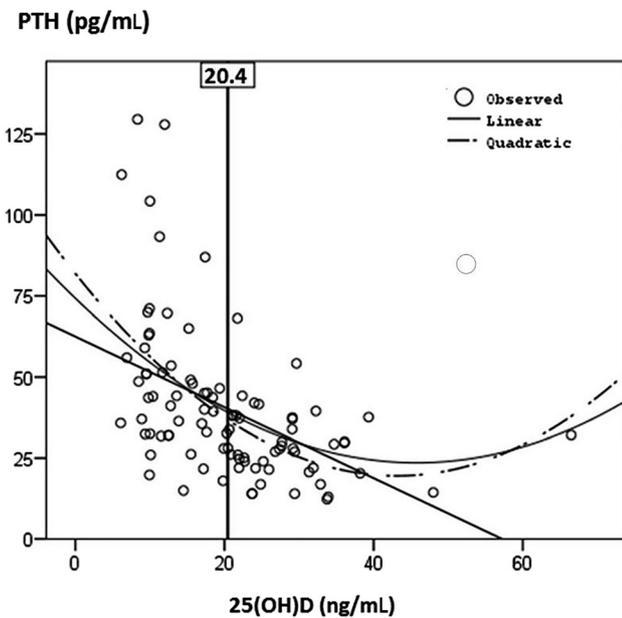

Figure 3: Graphical representation of vitamin 25(OH)D level which demonstrates maximal suppression of parathormone (PTH) for 3–6 age group.

retrospective nature, our study could not evaluate these parameters.

In our study, the (25-OHD) levels were lower and PTH levels higher in females than in males (p<0.001; Table 1). While the mean (25-OHD) in Asian males was reported to be statistically higher than in females, no significant difference was found between genders in Caucasians [7]. We believe that the significant difference found in our series resulted from the style of dress, i.e., girls wear more clothing than boys. A lower mean (25-OHD) was also found in females in Saudi Arabia, where it was thought to depend on the style of dress and restriction of outdoor activities [8].

We found that the (25-OHD) value that decreases PTH below 88 pg/mL (upper limit of optimal) was 11.34 ng/mL and the (25-OHD) value in children that decreases the PTH below 65 pg/mL (upper limit of the optimal range in children) was 14.42 ng/mL. The (25-OHD) level that decreases PTH below 12 pg/mL (lower limit of optimal) was 26.61 ng/mL and the (25-OHD) level that corresponds to 15 pg/mL PTH was 26.17 ng/mL (Table 4). The (25-OHD) level that maximally suppressed PTH, defined as the (25-OHD) sufficiency limit in the literature, averaged 22.51 ng/mL with the curve estimation method (Table 5).

There are different views on the limit of (25-OHD) deficiency in children. In the United States, the Institute of Medicine, Endocrine Society and Society for Adolescent Health and Medicine adopt a deficiency limit of 20 ng/mL, while the American Academy of Pediatrics adopts a deficiency limit of 15 ng/mL. The multinational consensus expert panel on rickets adopts a deficiency limit of 12 ng/mL [9–11]. While the optimal (25-OHD) level in adults is controversial, most specialists agree that it should be at least 20 ng/mL [12]. The Institute of Medicine and National Osteoporosis Society adopted a deficiency limit of 20 ng/

mL [9, 13]. Even if (25-OHD) is increased, the (25-OHD) level at which PTH would not decrease and follow a straight line is in the range 30–44 ng/mL (75–110 nmol/dL) [14]. Generally, it is felt that a (25-OHD) level of 30 ng/mL will eliminate problems related to vitamin D deficiency [15]. Oems et al. reported that the value at which secondary hyperparathyroidism occurs was 12 ng/mL in older women [16]. Heaney et al. suggest that the lowest optimal (25-OHD) is the value at which hepatic 25 hydroxylase has no action and should be 35 ng/mL [17]. This value is close to the value of 30–32 ng/mL suggested by other researchers [18]. The results of studies examining the (25-OHD) level that realizes maximal suppression at PTH are variable, but the range is 27.5–30 ng/mL in adults [19]. In hypovitaminosis D, PTH is increased and intestinal calcium absorption is decreased; sufficient calcium absorption is not realized if (25-OHD) is lower than 4.4 ng/mL [20].

A high PTH is a main cause of morbidity. In a study of patients older than 65 years with hip fractures, serum (25-OHD) was below 12 and 12–20 ng/mL in 57.2 and 27.7%, respectively. A (25-OHD) level ≤12 ng/mL was adopted as high risk and values of 12–20 were adopted as medium risk [21]. (25-OHD) shows racial differences. Blacks living in the United States have a higher bone density and over risk of fracture. (25-OHD) bioavailability in blacks and whites is similar. However, the difference results from the fact that the protein that binds low (25-OHD) is more widespread in blacks [22]. According to data from the National Health and Nutrition Examination Survey (NHANES), (25-OHD) levels were lower than 20 ng/mL in 41.6% of the population older than 20 in the United States in 2005–2006. Values lower than 32 ng/mL were found in 70%. (25-OHD) was remarkably low in people who were not Caucasian, did not receive a high school education, were obese, had a low high-density lipoprotein level, suffered malnutrition and failed to consume milk daily [23].

The incidence of (25-OHD) deficiency is increasing globally. Values lower than 30 ng/mL are common in many regions. Values lower than 10 ng/mL are widespread in South Asia and Central Asia. According to NHANES, the average (25-OHD) level in the USA decreased from 30 to 24 ng/mL during 1988–2004 and from 24 to 19.9 ng/mL during 2004–2006 [24]. Most of those with low (25-OHD) levels have levels of 15–20 ng/mL, i.e. deficiency. Detailed tests are recommended for serum (25-OHD) values lower than 10 or 15 ng/mL as these pose a risk of rickets and osteomalacia.

Those living in the Northern Hemisphere are at risk as a result of spending more time indoors (lack of sun exposure) and decreased synthesis in the skin with ageing. Vitamin D intake also decreases in the elderly. For instance, the daily average vitamin D intake of postmenopausal women in France was 144 units [25]. In Turkey, the combined proportions of (25-OHD) insufficiency and deficiency were highest in spring (31.87%) and lowest in summer (13.12%) [26]. Here, in accordance with the literature, we found the highest (25-OHD) levels in summer and the lowest in the spring (Table 3). (25-OHD) levels are reported to be low in obese children, who require vitamin D supplementation [27]. As our study was retrospective, however, we could not obtain weight and height data on all patients and could not evaluate this.

When the patients were subdivided into age groups, PTH increased with age while (25-OHD) decreased with increasing age (Table 6) (p<0.001). The lower limit of (25-OHD) insufficiency compared with a PTH level of 15 pg/mL was 35.02, 23.20 and 26.19 ng/mL for 0–2, 3–6 and 7–18 years, respectively. The (25-OHD) deficiency cut-off corresponding to 65 pg/mL, which is the optimal paediatric upper limit of PTH, was 21.39, 15.33 and 13.34 ng/mL for 0–2, 3–6 and 7–18 years, respectively. The (25-OHD) level that maximally suppresses PTH was 31.20, 20.44 and 17.07 ng/mL for 0–2, 3–6 and 7–18 years, respectively. We obtained two different but similar cut-off values for (25-OHD) insufficiency by using two different statistical techniques for ages 0–2 and 3–6 years. No published study has reported vitamin D deficiency cut-offs according to age in childhood. Interestingly, the (25-OHD) level tended to decrease with increasing age. Because of the rapid growth and ossification in infants and early childhood, vitamin D requirements are high and the sufficiency level may be higher. Nevertheless, studies with more cases are required. Based on the statistical analyses, the (25-OHD) deficiency and insufficiency cut-offs are 21–31, 15–21 and 13–17 ng/mL for 0–2, 3–6 and 7–18 years, respectively. Our retrospective study limitations are our lack of knowledge of the patients' calcium and vitamin D intake and of their body mass indices.

Conclusion

The (25-OHD) deficiency limit should be 14 ng/mL and insufficiency level 23 ng/mL for children living in Istanbul. There are no current data on this. The cut-off values of (25-OHD) for the deficiency (lower value) and insufficiency (range) according to age are 21–31, 15–21 and 13–17 ng/mL for 0–2, 3–6 and 7–18 years, respectively. In our series, based on the 14 ng/mL (25-OHD) deficiency limit, 80 patients (18.9%) had deficiency, while based on the 23 ng/mL vitamin D insufficiency value, 195 (46.2%) patients were

vitamin D insufficient. More studies with more subjects are needed to confirm these findings.

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