Clinical Pediatric Endocrinology

Vol.34 / No.2
April 2025
pp 115–120

Original Article

Cutoff value of serum 25-hydroxyvitamin D leading to vitamin D deficiency for children in Japan

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Highlights

- The 25(OH)D cutoff values for VDD are determined variously.
- Low 25(OH)D levels do not always cause clinical symptoms.
- The 25(OH)D cutoff value leading to manifest VDD for children in Japan is 37.5 nmol/L.

Abstract. The 25-hydroxyvitamin D [25(OH)D] level and clinical symptoms are used to diagnose vitamin D deficiency (VDD). The current 25(OH)D cutoff value is based on biochemical findings, such as elevated parathyroid hormone (PTH) levels, rather than clinical symptoms. However, low 25(OH)D levels do not necessarily produce clinical symptoms. The present study proposed a 25(OH)D cutoff value for diagnosing manifest VDD, defined as VDD that is diagnosable based on either clinical symptoms, such as rickets and/or hypocalcemia (symptomatic VDD), or biochemical findings, such as elevated PTH and alkaline phosphatase levels (biochemical VDD). One hundred and eighty participants aged 0–15 yr with suspected VDD were enrolled, and receiver operating characteristic curve analysis was performed. Sixty-seven and ten patients had symptomatic and biochemical VDD, respectively. A chemiluminescent immunoassay, which demonstrated good correlation with liquid chromatography-tandem mass spectrometry, determined the 25(OH)D cutoff value for manifest VDD to be 37.5 nmol/L (15.0 ng/mL), with a sensitivity and specificity of 81% and 97%, respectively. Twenty percent (19/94) of participants with 25(OH)D ≤ 37.5 nmol/L were asymptomatic. In cases with 25(OH)D ≤ 37.5 nmol/L, a low urinary calcium-to-creatinine ratio was a risk factor for manifest VDD. In conclusion, the 25(OH)D cutoff value leading to manifest VDD for children in Japan was 37.5 nmol/L.

Key words: 25(OH)D, hypocalcemia, rickets, ROC, vitamin D deficiency

Received: September 30, 2024 Accepted: February 1, 2025 Advanced Epub: March 5, 2025
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Introduction

Vitamin D is essential for bone and calcium metabolism, and its deficiency can produce childhood symptoms, such as rickets and hypocalcemia. The 2016 global consensus recommendations on the prevention and management of nutritional rickets (1) defined vitamin D insufficiency and deficiency by a 25-hydroxyvitamin D [25(OH)D] level of 30.0–50.0 nmol/L (12.0–20.0 ng/mL) and ≤ 30.0 nmol/L (12.0 ng/mL), respectively. While the Japanese Society for Pediatric Endocrinology [JSPE (http://jspe.umin.jp/)] has adopted 25(OH)D < 37.5–50.0 nmol/L (15.0–20.0 ng/mL) as the criterion for vitamin D deficiency (VDD) in Japanese children, this value is not based on evidence derived from the Japanese population. Some children do not manifest clinical symptoms or biochemical abnormalities, even when their 25(OH)D levels fall within the deficiency range. In fact, when Kubota *et al*. (2) reported the first nationwide survey of VDD in Japanese children, radiographic signs of rickets were not required for diagnosis.

Various methods are currently used to measure 25(OH)D levels. However, to establish the 25(OH)D cutoff value for VDD, a validated assay referencing the liquid chromatography-tandem mass spectrometry (LC-MS/MS) value is required. Furthermore, no study has employed receiver operating characteristic (ROC) curve analysis, a rational method for determining this cutoff, to establish 25(OH)D-based criteria for diagnosing VDD.

Therefore, the present study aimed to determine the 25(OH)D cutoff value for diagnosing manifest VDD. We categorized VDD into two types: 1) symptomatic VDD, that is, VDD with clinical symptoms such as rickets and/or hypocalcemia, and 2) biochemical VDD, which is diagnosed solely on the basis of biochemical findings. These two subgroups are together referred to herein as "manifest VDD." Given that no previous guidelines have adopted LC-MS/MS data, our cutoff value was converted to LC-MS/MS data.

Participants and Methods

Participants

This retrospective study enrolled participants aged 0–15 yr with suspected VDD whose 25(OH)D levels were measured between April 2013 and March 2018 at four participating hospitals: Tokyo Metropolitan Children's Medical Center, Niigata University, Sapporo Medical University, and Osaka City General Hospital. The first value obtained from the 25(OH)D measurement was used.

Exclusion criteria

The exclusion criteria encompassed the following: (i) the administration of supplements or drugs potentially influencing bone metabolism, including vitamin D, calcium, supplements, glucocorticoids, and growth hormones, either at or before their 25(OH)D measurement; (ii) a condition potentially affecting calcium and bone metabolism, such as 22q11.2 deletion syndrome, hypoparathyroidism, pseudohypoparathyroidism, hypophosphatemic rickets, transient hyperphosphatasemia, drug-induced hyperphosphatasemia/rickets, hypophosphatasia, renal insufficiency such as Fanconi syndrome, or metabolic bone disease of prematurity; and (iii) the presence of genu varum/valgum due to an orthopedic disorder such as Blunt disease.

Definitions of diagnoses

We defined "manifest VDD" irrespective of 25(OH)D levels; VDD is clinically diagnosable based on either symptoms, such as genu varum, or biochemical findings. In this study, manifest VDD was further divided into a symptomatic VDD group, defined by the presence of clinical symptoms, and a biochemical VDD group, defined by the asymptomatic elevation of ALP and intact PTH (iPTH). Non-VDD was defined by the fulfillment of the following criteria: 1) absence of rickets, 2) absence of hypocalcemia, and 3) normal ALP and iPTH levels. Hypocalcemia was defined as an albumin-corrected total serum calcium < 8.4 mg/dL [total serum calcium (mg/dL) + 4 – serum albumin (g/dL)]. **Table 1** shows the classification of participants according to the presence or absence of hypocalcemia.

Diagnosis of rickets and hypocalcemia due to VDD

Manifest VDD was diagnosed based on clinical symptoms without relying on 25(OH)D levels. All participants underwent an X-ray assessment of rickets, which was diagnosed on the basis of radiographically visible features of the wrists or knees (3) by the authors, who are pediatric endocrinologists certified by the Japan Endocrine Society (http://www.j-endo.jp/). Healing rickets was identified retrospectively based on the findings of Chang *et al*. (4). Hypocalcemia was defined as a corrected serum calcium level of < 8.4 mg/dL. iPTH elevation was defined as iPTH ≥ 65.0 pg/mL. ALP elevation was defined as ALP ≥ 420 IU/L within the age of 1 yr and ≥ 350 IU/L after the age of ≥ 1 yr using the International Federation of Clinical Chemistry (IFCC) and Laboratory Medicine reference unit.

Medical history and laboratory data

Risk factors for manifest VDD, such as breastfeeding, maternal VDD, dietary restrictions (e.g., food allergies), unbalanced diets (e.g., religion- or culture-related dietary restrictions), chronic diarrhea, lack of sun exposure, preterm birth, and cholestatic disease, were assessed. Serum levels of 25(OH)D, calcium, ALP, albumin, iPTH, urinary calcium, and creatinine were also measured.

doi: 10.1297/cpe.2024-0070

Table 1. Classification of participants

Hypocalcemia	Abnormal X-ray findings	Clinical symptoms and biochemical findings	Classification	n
(+)	(+)	Rickets	Symptomatic VDD	9
		Healing rickets	Symptomatic VDD	1
	(–)	Elevation of both ALP and intact-PTH	Symptomatic VDD	6
		The others *	Symptomatic VDD	0
(–)	(+)	Rickets	Symptomatic VDD	51
		Healing rickets	Excluded	13
	(–)	Elevation of both ALP and intact-PTH	Biochemical VDD	10
		The others *	Non-VDD	90

* 'The others' indicates cases without findings of rickets, healing rickets, or elevated ALP and iPTH levels. VDD, vitamin D deficiency; ALP, alkaline phosphatase; iPTH, intact parathyroid hormone.

Biochemical analysis

Radioimmunoassay (RIA; 25OH-Vitamin D total-RIA-CT, DiaSource, Belgium), double-antibody radioimmunoassay (RIA2; 25-Hydroxyvitamin D 125I RIA Kit, DiaSorin Inc., Italy), chemiluminescent enzyme immunoassay (CLEIA; Lumipulse® 25-OH vitamin D, Fujirebio, Japan), and chemiluminescent immunoassay (CLIA; LIAISON® 25 hydroxy vitamin D TOTAL, DiaSorin Inc., Italy) were used to measure 25(OH)D. Because CLIA is one of the most commonly used assays in Japan, the RIA, RIA2, and CLEIA findings were converted into CLIA-equivalent values (Supplementary Table 1). Furthermore, a previous study reported a strong positive correlation between 25(OH)D values obtained by CLIA and those obtained by LC-MS/MS (CLIA nmol/L = 0.98 × LC-MS/MS nmol/L+2.10) (5). Serum iPTH levels were measured using ECLIA, whereas serum calcium, phosphate, urinary calcium, and creatinine levels were measured using standard colorimetric methods. The ALP value obtained using the Japan Society of Clinical Chemistry reference units was multiplied by 0.35 and converted to IFCC and Laboratory Medicine reference units.

Statistical analysis

All statistical analyses were performed using EZR ver. 4.3.1 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a modified version of R commander (The R Foundation for Statistical Computing, Vienna, Austria) (6), was designed to add statistical functions frequently used in biostatistics. All descriptive results were expressed as the median and minimum to maximum values. Owing to the skewed distribution of the outcome measurements, the pairwise Mann-Whitney U test was used to analyze age, 25(OH)D level, iPTH level, and the urinary calcium to creatinine ratio (UCaCrR). $P < 0.05$ was considered to indicate statistical significance. The highest sensitivity and specificity of ROC curve analysis were used to determine the 25(OH)D cutoff value for manifest VDD.

Ethical statement

This study was approved by the Ethics Committee of Tokyo Metropolitan Children's Hospital (approval code: H30b-24) and was conducted in accordance with the principles of the Declaration of Helsinki. All patients consented to participate using the opt-out method at each institution.

Results

Characteristics

In total, 605 participants had their 25(OH)D levels measured in the study period, and 408 participants were excluded for rickets or hypocalcemia due to causes other than low 25(OH)D (e.g., hypophosphatemic rickets or hypoparathyroidism) and/or those who had previously received treatment. Seventeen participants without iPTH measurements were also excluded. The remaining 180 participants were analyzed; of these, 94 (52.2%) were male, and the median age at 25(OH)D measurement was 1.8 yr (range: 0.1–14.8 yr). The attending physician suspected vitamin D deficiency due to growth failure, genu varum, and hypocalcemia. Sixty-seven participants received a diagnosis of symptomatic VDD, and ten had biochemically diagnosable VDD. Thirteen participants had healing rickets, and 90 participants were categorized as non-VDD.

All participants with symptomatic VDD had at least one of the previously mentioned risk factors for low 25(OH)D levels, such as breastfeeding. In contrast, the proportions of participants with biochemical VDD and non-VDD who had at least one risk factor were 80% (8/10) and 39% (35/90), respectively (Supplementary Table 2).

The median 25(OH)D values for symptomatic VDD, biochemical VDD, and non-VDD were 18.3 nmol/L (range: 7.8–38.8 nmol/L), 16.3 nmol/L (range: 10.0–56.5 nmol/L) and 48.5 nmol/L (range: 12.5–90.3 nmol/L), respectively (**Table 2**). The 25(OH)D levels in the manifest VDD (symptomatic and biochemical VDD) and non-VDD groups, shown in the box-and-whisker

doi: 10.1297/cpe.2024-0070

plot, differed significantly (**Fig. 1a**).

The cutoff value for 25-hydroxyvitamin D

ROC curve analysis was performed to determine the cutoff value for 25(OH)D after excluding the participants with healing rickets. Subjectivity in the definition of healing rickets was unavoidable. After comparing the 25(OH)D values of the manifest VDD (n = 77) and non-VDD (n = 90) groups, the cutoff value for the former was determined to be 37.5 nmol/L (15.0 ng/mL), with a sensitivity of 81% and a specificity of 97% (area under the curve [AUC]: 0.929, 95% confidence interval [CI]: 0.890–0.968) (**Fig. 1b**). This cutoff value was converted to 36.1 nmol/L using LC-MS/MS data. Conflating biochemical VDD with non-VDD did not show a statistically significant difference in the ROC results; there is controversy about how to manage patients with mild VDD, who have only biochemical abnormalities like the biochemical VDD group in this study. When an international diagnostic criterion of 30.0 nmol/L was used as the cutoff value, the sensitivity and specificity were 89% and 86%, respectively (data not shown).

Differences in UCaCrR of participants with 25(OH)D ≤ 37.5 nmol/L between the non-VDD group and the manifest VDD group

Of the 94 cases with 25(OH)D ≤ 37.5 nmol/L, 20% (19/94) were categorized as non-VDD. **Table 3**, which compares the biochemical data of participants with 25(OH)D ≤ 37.5 nmol/L for identifying the predictors of manifest VDD, demonstrates a significant difference in the 25(OH)D value between the non-VDD and manifest VDD groups. Furthermore, the present study found a median UCaCrR of 0.14 and 0.05 in the non-VDD and manifest VDD groups, respectively ($P < 0.05$) (**Table 3**). A similar result was obtained when all the analyses were repeated after excluding participants with hypocalcemia because UCaCrR may be affected by hypocalcemia

Table 2. Median 25(OH)D value and range for each group

	25(OH)D* (nmol/L) [range]
All cases (n = 180)	32.1 [7.8–90.3]
Non-VDD (n = 90)	48.5 [12.5–90.3]
Healing rickets (n = 13)	28.5 [16.5–79.3]
VDD (n = 77)	18.0 [7.8–56.5]
Symptomatic VDD (n = 67)	18.3 [7.8–38.8]
Rickets (n = 51)	19.3 [10.3–38.8]
Rickets and hypocalcemia (n = 9)	15.0 [7.8–27.0]
Hypocalcemia (n = 6)	12.0 [7.8–21.5]
Healing rickets and hypocalcemia (n = 1)	8.3 [NA]
Biochemical VDD (n = 10)	16.3 [10.0–56.5]

25(OH)D, 25-hydroxyvitamin D; VDD, vitamin D deficiency. *Data are presented as median [range].

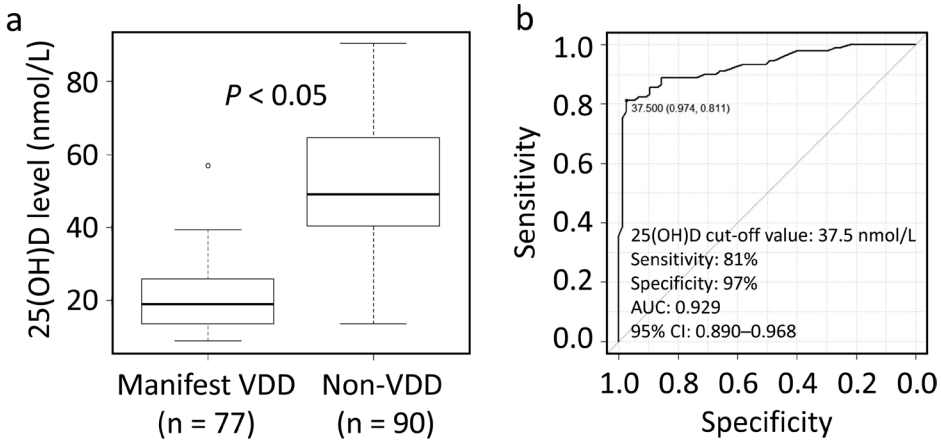

Fig. 1. (a) Box and whisker plot of serum 25(OH)D levels in the manifest VDD and non-VDD groups. The central line in the box indicates the median; the top and bottom of the box indicate the quartile boundaries; the vertical bars indicate the minimum and maximum values within 1.5 times the interquartile range of the quartile boundary; a circle indicates that the value is more extreme. (b) Results of the ROC curve analysis. The 25(OH)D cutoff value for the manifest VDD group was 37.5 nmol/L, with a sensitivity and specificity of 81% and 97%, respectively. ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval.

doi: 10.1297/cpe.2024-0070

(Supplementary Table 3). Comparing symptomatic and biochemical VDD in the manifest VDD groups, UCaCr was lower in symptomatic VDD than in biochemical VDD (**Table 4**).

Discussion

In the present study, the 25(OH)D cutoff value for manifest VDD was 37.5 nmol/L (15.0 ng/mL), which was close to the value stipulated in the criteria for diagnosing VDD according to the global consensus (30.0 nmol/L, (1)) and the JSPE (37.5–50.0 nmol/L). The cutoff value was converted to 36.1 nmol/L using LC-MS/MS data. Furthermore, this 25(OH)D level for diagnosing manifest VDD was determined using ROC analysis. The present study is the first to investigate the 25(OH)D cutoff value for VDD based on clinical symptoms and/or biochemical markers in a pediatric population in Japan.

It is meaningful to reveal that 37.5 nmol/L (15.0 ng/mL) is the cutoff value for manifest symptoms due to low 25(OH)D. In contrast, the latest Endocrine Society Clinical Practice Guideline (7) advises against routine 25(OH)D testing in all populations because there is no evidence defining the optimal target level of 25(OH)D required for disease prevention. The participants in this study were suspected of having vitamin D deficiency by their attending physicians. Therefore, patients with significantly low 25(OH)D in such a population should be treated.

The present study also revealed that, in the participants with 25(OH)D ≤ 37.5 nmol/L, the UCaCrR as well as 25(OH)D was lower in the manifest VDD group than in the non-VDD group. This finding of urine calcium may be related to the total body calcium amount. Sempos *et al*. revealed that as calcium intake increased, the odds ratio of rickets decreased, even with similar levels of 25(OH)D (8). Miyai *et al*. reported that the UCaCrR can be influenced by calcium supply and that a ratio < 0.1 was useful for detecting secondary hyperparathyroidism in patients with VDD (9). A recent study advocated the use of a combination of vitamin D and calcium to treat nutritional rickets in children (10). Taken together, education regarding dietary calcium intake and supplementation may facilitate the treatment of VDD in the presence of a low UCaCrR.

The duration of low 25(OH)D levels is another factor that affects the manifestation of VDD. Indeed, in the present study, participants in whom biliary atresia was diagnosed shortly after the onset of cholestasis had neither rickets nor hypocalcemia, despite having low 25(OH)D levels (data not shown).

One of the strengths of the present study was its design. Only cases with all the parameters necessary for diagnosing VDD were collected and analyzed. This study started without a cutoff for 25(OH)D rather than resorting to the previously published definition of VDD,

Table 3. Comparisons in participants with low 25(OH)D * between the non-VDD and manifest VDD groups

	Non-VDD (n = 19)	Manifest VDD (n = 75)	P-value
Age (mo)	17 [1–175]	19 [1–143]	0.75
25(OH)D (nmol/L)	24.8 [12.5–37.5]	17.8 [7.8–36.8]	< 0.05
Ca (mg/dL)	9.8 [8.7–10.9]	9.3 [5.6–10.9]	< 0.05
P (mg/dL)	5.1 [2.8–6.3]	4.3 [1.9–7.5]	< 0.01
ALP (IU/L)	395 [105–1229]	803 [273–3165]	< 0.05
iPTH (pg/mL)	31.0 [9.0–66.5]	221.0 [36.0–776.0]	< 0.05
UCaCrR	0.14 [0.01–0.58] (n = 14)	0.05 [0.00–0.70] (n = 58)	< 0.05

Values are reported as medians and ranges. VDD, vitamin D deficiency; 25(OH)D, 25-hydroxyvitamin D; ALP, alkaline phosphatase; iPTH, intact parathyroid hormone; UCaCrR, urinary calcium-to-creatinine ratio. * 25(OH)D ≤ 37.5 nmol/L.

Table 4. Comparisons in participants with low 25(OH)D* between symptomatic and biochemical VDD

	Symptomatic VDD (n = 66)	Biochemical VDD (n = 9)	P-value
Age (mo)	20 [1–143]	2 [1–17]	< 0.05
25(OH)D (nmol/L)	18.2 [7.8–36.8]	15.0 [10.0–30.8]	0.41
Ca (mg/dL)	9.25 [5.6–10.9]	9.6 [8.9–10.7]	0.09
P (mg/dL)	4.2 [1.9–6.2]	5.6 [3.6–7.5]	< 0.01
ALP (IU/L)	795 [273–3165]	817 [471–1572]	0.41
iPTH (pg/mL)	228.5 [36–776]	89.9 [66–483]	< 0.05
UCaCrR	0.03 [0.00–0.43]	0.23 [0.02–0.70]	< 0.01

Values are reported as medians and ranges. VDD, vitamin D deficiency; 25(OH)D, 25-hydroxyvitamin D; ALP, alkaline phosphatase; iPTH, intact parathyroid hormone; UCaCrR, urinary calcium-to-creatinine ratio. * 25(OH)D ≤ 37.5 nmol/L.

doi: 10.1297/cpe.2024-0070

which is based on the 25(OH)D value. Although several cutoff values of serum 25(OH)D for diagnosing VDD have been proposed, the topic remains controversial (11). The present study was also the first to determine the 25(OH)D cutoff value for manifest VDD using ROC curve analysis, a rational method for determining the probability of VDD occurrence. Furthermore, the correlation between the currently-used assays and LC-MS/MS data were provided. Finally, the large number of 25(OH)D measurements included in the initial analysis (180 samples) constitutes another strength.

Our study had several limitations. First, it was retrospective; calcium intake was not analyzed, and only participants with UCaCrR measurements were included in the analysis of urinary calcium. However, it is practically impossible to assess calcium or other nutrients in a retrospective study. To date, only Sempos *et al*. have attempted to clarify the relationship between calcium intake and nutritional rickets development at each 25(OH)D level (8). Second, our study was based on data derived from the Japanese population, which is largely homogeneous; thus, our findings may not be generalizable to other ethnicities. For example, low 25(OH)D levels, indicative of VDD, are common among infants in Japan, especially those who are breastfed, and a low maternal 25(OH)D status is a risk factor for infant VDD in some countries (12). In contrast to other developed nations where routine vitamin D supplementation is recommended (13), vitamin D supplementation is not routinely prescribed to prevent VDD during infancy in Japan.

Conclusion

Using CLIA, the present study found that the 25(OH)D cutoff value for manifest VDD was 37.5 nmol/L (15.0 ng/mL) for children in Japan. However, because this study was retrospective, future prospective studies are required to verify these findings.

Conflict of interests: The authors declare no potential conflicts of interest.

Acknowledgments

We are indebted to Mr. James R. Valera for his assistance in editing this manuscript.

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