

Vitamin D distribution by month, sex, and season in Turkey, Niğde province: A retrospective cohort study

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Ethics Committee Approval

The study was approved by Non-invasive Clinical Research Ethics Committee of Niğde Ömer Halisdemir University (Date: April 14, 2023, no: 2023/15).

All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest

No conflict of interest was declared by the authors.

Financial Disclosure

The authors declared that this study has received no financial support.

Published

2024 March 19

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Abstract

Background/Aim: Epidemiological investigations consistently indicate a widespread deficiency and insufficiency of vitamin D on a global scale. Vitamin D deficiency can lead to various acute and chronic diseases, including pre-eclampsia, autoimmune disorders, cardiovascular diseases, certain cancers, type 2 diabetes, and neurological disorders. However, the relationship between vitamin D status and its implications for global and public health has not been comprehensively explored. Notably, the differing clinical decision thresholds for diagnosing vitamin D deficiency and insufficiency established by various associations can create diagnostic confusion. Therefore, our study aimed to assess the distribution of vitamin D levels in Niğde province, considering variations by month, gender, and season, with respect to the clinical decision thresholds defined by different associations.

Methods: The study sample comprised 57,731 cases (71% women and 19% men) admitted to our hospital between January 2021 and December 2022. We retrospectively evaluated 25-hydroxyvitamin D (25(OH)D) levels based on months, seasons, age, and gender. Additionally, we examined 25(OH)D levels separately using the clinical decision thresholds set by the Vitamin D Council, the Endocrine Society, and the Food and Nutrition Board. Patients with chronic renal insufficiency, hepatic insufficiency, and gastrointestinal malabsorption were excluded from the study, encompassing patients of all age groups. Furthermore, we categorized patients into different age decades and analyzed their vitamin D levels. We compared the same months in 2021 and 2022, monitoring changes in vitamin D levels throughout the year. Vitamin D levels were measured using the electrochemiluminescence assay (ECLIA) on a Roche Cobas E801 instrument.

Results: When comparing the same months in 2021 and 2022, there was no statistically significant decrease or increase in 25(OH)D levels (The P-values for January and December were 0.066, 0.395, 0.907, 0.465, 0.705, 0.541, 0.625, 0.860, 0.695, 0.549, 0.892, and 0.838, respectively). Vitamin D insufficiency was observed in 70.3% of women and 29.7% of men. Participants under one year of age exhibited the highest mean 25(OH)D level (34.9 ng/mL), while participants between 20 and 29 years of age had the lowest mean 25(OH)D level (15.7 ng/mL). The lowest mean 25(OH)D level was recorded in April 2022 (15.6 ng/mL), whereas the highest mean 25(OH)D level was observed in July 2021 (22.7 ng/mL). There was a slight negative correlation between age and 25(OH)D levels ($r=-0.038$, $P<0.001$). The Vitamin D Council classification identified the highest number of patients with vitamin D deficiency ($n=50,833$; 88%). The Food and Nutrition Board included the lowest number of patients with vitamin D deficiency ($n=15,049$; 26.1%).

Conclusion: Vitamin D deficiency is prevalent in Niğde province, particularly among women, and remains a significant public health concern. We advocate for the adoption of a unified clinical decision threshold and the expansion of the national vitamin D supplementation program to encompass adolescents and adults.

Keywords: vitamin D, phosphorus, calcium, vitamin D deficiency

Introduction

Vitamin D plays a crucial role in maintaining the balance of phosphorus and calcium in the body. It is also a fat-soluble vitamin essential for the health of bones, teeth, and muscles [1]. Vitamin D deficiency is a global public health concern with a high prevalence and adverse effects on both musculoskeletal and nonskeletal health [2]. A deficiency in vitamin D is closely associated with an increased risk of various conditions, including infections, type 1 and type 2 diabetes mellitus, obesity, cardiovascular disease, asthma, breast cancer, ovarian cancer, prostate cancer, colon cancer, and certain neurological diseases [1].

The cholesterol-like precursor molecule (7-dehydrocholesterol) found in skin epidermal cells can undergo transformation into pre-vitamin D, which, upon exposure to UV-B radiation (wavelength 290-315 nm), is isomerized into vitamin D3. Vitamin D3, in its initial form, is biologically inactive and requires enzymatic conversion to become active. Initially, it undergoes a process of 25-hydroxylation in the liver to become 25-hydroxyvitamin D (25(OH)D), which serves as the primary circulating form of vitamin D. Subsequently, in the kidneys, it is further converted through 1-alpha-hydroxylation to become 1,25(OH)2D, also known as calcitriol [3].

The level of 25(OH)D in serum and plasma serves as a marker reflecting the overall vitamin D status [4]. Although various organizations establish different clinical thresholds for assessing 25(OH)D status, many experts consider levels below 20 ng/mL as indicative of vitamin D insufficiency [5]. Interpretation of vitamin D results can vary among experts due to these differing clinical thresholds, making standardization and interpretation challenging [5]. Furthermore, vitamin D levels are influenced by factors such as age, sex, angle of sunlight exposure, subcutaneous synthesis, and the number of sunny days [6].

Vitamin D deficiency poses a significant global and societal concern, but the varying clinical thresholds adopted by different medical associations can lead to confusion when assessing patient outcomes. To address the issues stemming from these disparities, we conducted a retrospective analysis of two years' worth of patient data in Niğde Province. Our evaluation of vitamin D deficiency took into account factors such as age, gender, age deciles, seasons, months, and the diverse clinical thresholds established by various organizations.

Materials and methods

Research design

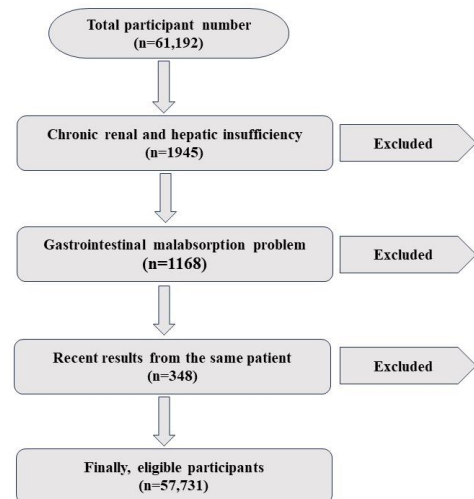
Our study is a retrospective cohort analysis. The sample consisted of 57,731 cases, with 40,966 (71.0%) being women and 16,765 (29%) being men, who were admitted to our hospital between January 2021 and December 2022 in Niğde, Turkey (latitude 37° 57' 59.99" N). We grouped and evaluated 25(OH)D levels with respect to age, age decades, sex, season, and months. Additionally, we conducted a correlation analysis to examine the relationship between age and 25(OH)D levels.

Vitamin D insufficiency and deficiency were assessed with consideration to different clinical decision points, including those established by the Vitamin D Council (VDC), the

Endocrine Society (ES), and the Food and Nutrition Board (FNB). For our assessment, we utilized the clinical decision points defined by the ES, which categorize vitamin D deficiency as 0-20 ng/mL and vitamin D insufficiency as 21-29 ng/mL.

Given the retrospective nature of our cohort study, we were unable to ascertain whether the cases had used vitamin D supplements. We have addressed this limitation in the corresponding section. To maintain the integrity of our study, we excluded cases with chronic renal and hepatic insufficiency, as well as those with gastrointestinal malabsorption. Additionally, patients with recent repeat test results were excluded from the analysis. Diagnosis information for the patients was obtained from the hospital information system (Figure 1).

Figure 1: Flowchart of the study



Patients of all age groups were included in the study. Our research was approved by the Niğde Ömer Halisdemir University Non-Invasive Clinical Research Ethics Committee (Date: April 14, 2023, Approval number: 2023/15).

Laboratory analysis

Blood samples were collected in anticoagulant-free tubes for the measurement of serum 25(OH)D levels. These blood samples were then subjected to centrifugation at 2000g for 10 min at 25°C to obtain serum samples. Subsequently, these serum samples were analyzed using electrochemiluminescence (ECLIA) on a Cobas E801 instrument by Roche Diagnostic.

The measurement range for serum 25(OH)D levels was 3 to 100 ng/mL. Any measurements exceeding 100 ng/mL were diluted and adjusted using a multiplication factor.

Based on the analysis of five-level human serum pools by the manufacturer, which had mean concentrations of 10.5, 21.1, 24.9, 54.9, and 94.3 ng/mL, the coefficient of variation (CV%) for intra-study reproducibility was 7.4%, 4.6%, 3.9%, 3.1%, and 2.8%, respectively. The overall CV% values for reproducibility in the same serum pools were 8.9%, 5.9%, 4.9%, 3.8%, and 3.8%, respectively.

The limit of detection (LOD) was determined to be 3 ng/mL, and the limit of quantitation (LOQ) was determined to be 5 ng/mL using the Clinical and Laboratory Standards Institute (CLSI) EP17 A2 method.

Vitamin D interpretation

To interpret vitamin D levels, we primarily relied on the clinical decision points established by different organizations. According to the ES, levels below 20 ng/mL are classified as vitamin D deficiency, levels between 21 and 29 ng/mL are

categorized as vitamin D insufficiency, levels between 30 and 100 ng/mL are considered optimal, and levels above 100 ng/mL are regarded as potentially harmful [7].

In reference to the VDC, levels below 30 ng/mL are defined as vitamin D deficiency, levels between 31 and 39 ng/mL are labeled as vitamin D insufficiency, levels between 40 and 80 ng/mL are designated as optimal, levels between 81 and 149 ng/mL are categorized as vitamin D excess, and levels above 150 ng/mL are considered potentially harmful [5].

Considering the FNB guidelines, levels below 11 ng/mL are recognized as vitamin D deficiency, levels between 12 and 20 ng/mL are categorized as vitamin D insufficiency, levels between 21 and 100 ng/mL are considered optimal, and levels above 100 ng/mL are deemed potentially harmful [8].

Statistical analysis

Statistical analysis was conducted using SPSS for Windows, version 15.0, with a significance level set at 0.05. Descriptive statistics, including mean, median, minimum, maximum, standard error of the mean, and percentages, were employed to summarize the data. To assess normality, the Shapiro-Wilk test was applied, revealing that the data did not follow a normal distribution. Consequently, pairwise comparisons were conducted using the Mann-Whitney U test.

To explore the relationship between age and vitamin D levels, Spearman’s correlation coefficient was calculated. Power analysis was performed using G*power 3.1.9.7, with a significance level (α) of 0.05 and a target power of 95%.

Results

Statistical analysis was conducted using SPSS for Windows, version 15.0, with a significance level set at 0.05. Descriptive statistics, including mean, median, minimum, maximum, standard error of the mean, and percentages, were employed to summarize the data. To assess normality, the Shapiro-Wilk test was applied, revealing that the data did not follow a normal distribution. Consequently, pairwise comparisons were conducted using the Mann-Whitney U test.

To explore the relationship between age and vitamin D levels, Spearman’s correlation coefficient was calculated. Power analysis was performed using G*power 3.1.9.7, with a significance level (α) of 0.05 and a target power of 95%.

According to the VDC, none of our participants had 25(OH)D levels above 150 ng/mL. However, in accordance with the ES and the FNB guidelines, eight participants exhibited 25(OH)D levels that could potentially have a toxic effect. Across all three organizations, both vitamin D deficiency and insufficiency were more prevalent among female participants than their male counterparts. The classification by the VDC indicated the highest number of participants with vitamin D deficiency (n=50,833, 88%). In contrast, the FNB identified the lowest number of patients with vitamin D deficiency (n=15,049, 26.1%). This discrepancy is due to the fact that the VDC employs a broader range for defining vitamin D deficiency (0-30 ng/mL) compared to the ES and the FNB.

Table 1: Distribution of 25(OH)D levels by month and sex

Months	n	Sex distribution		Mean(SEM) 25(OH)D(ng/mL)	P-value
		Female	Male		
January 2021	2121	66.8%	34.2%	19.5 (0.24)	0.066
January 2022	2229	69.9%	30.1%	17.9 (0.24)	
February 2021	2047	69.9%	30.1%	19.7 (0.25)	0.395
February 2022	2376	70.5%	29.5%	16.0 (0.23)	
March 2021	2410	70.9%	29.1%	19.9 (0.24)	0.907
March 2022	2990	72.3%	27.7%	16.3 (0.24)	
April 2021	1739	71.6%	28.4%	18.0 (0.27)	0.465
April 2022	2792	68.9%	31.1%	15.6 (0.25)	
May 2021	1154	68.9%	31.1%	19.7 (0.34)	0.705
May 2022	2625	71.8%	28.2%	17.7 (0.33)	
June 2021	2311	71.7%	28.3%	20.1 (0.22)	0.541
June 2022	3242	70.6%	29.4%	20.1 (0.22)	
July 2021	1716	70.9%	29.1%	22.7 (0.26)	0.625
July 2022	2115	70.8%	29.2%	22.6 (0.27)	
August 2021	1778	71.4%	28.6%	21.4 (0.24)	0.860
August 2022	3003	69.4%	30.6%	23.1 (0.26)	
September 2021	1829	71.2%	28.7%	21.9 (0.25)	0.695
September 2022	3226	72.4%	27.6%	22.0 (0.24)	
October 2021	1739	73.7%	26.3%	20.5 (0.25)	0.549
October 2022	2824	71.6%	28.4%	21.7 (0.23)	
November 2021	2178	68.7%	31.3%	18.9 (0.22)	0.892
November 2022	3580	71.7%	28.3%	19.9 (0.20)	
December 2021	2318	71.6%	28.4%	17.2 (0.22)	0.838
December 2022	3389	71.9%	28.1%	17.9 (0.21)	

Table 2: Vitamin D Levels according to three organization

Vitamin D Council					
Sex	Deficient 0-30 ng/mL	Insufficient 31-39 ng/mL	Sufficient 40-80 ng/mL	Excess 81-149 ng/mL	Possible harm >150 ng/mL
Female (n)	36,503	2776	1570	117	-
%	71.80%	62.90%	67.40%	76.50%	-
Male (n)	14,330	1638	761	36	-
%	28.20%	37.10%	32.60%	23.50%	-
Total	50,833	4414	2331	153	-
In terms of females (n=40,966)	36,503 (89.10%)	2776 (6.80%)	1570 (3.80%)	117 (0.30%)	-
In terms of males (n=16,765)	14,330 (85.50%)	1638 (9.80%)	761 (4.50%)	36 (0.20%)	-
Endocrine Society					
Gender	Deficient 0-20 ng/mL	Insufficient 21-29 ng/mL	Sufficient 30-100 ng/mL	Possible harm >100 ng/mL	
Female (n)	27,658	8354	4945	4	
%	70.30%	60.90%	63.80%	50.00%	
Male (n)	8598	5366	2802	4	
%	23.70%	39.10%	36.20%	50.00%	
Total	36,256	13,720	7747	8	
In terms of females (n=40,966)	27,658 (67.50%)	8354 (20.40%)	4945 (12.09%)	4 (0.01%)	
In terms of males (n=16,765)	8598 (51.28%)	5366 (32.00%)	2802 (16.70%)	4 (0.02%)	
Food and Nutrition Board					
Gender	Deficient 0-11 ng/mL	Insufficient 12-20 ng/mL	Sufficient 21-100 ng/mL	Possible harm >100 ng/mL	
Female (n)	12,894	14,764	13,299	4	
%	85.70%	69.70%	61.90%	50.00%	
Male (n)	2155	6425	8186	4	
%	14.30%	30.30%	38.10%	50.00%	
Total	15,049	21,189	21,485	8	
In terms of females (n=40,966)	12,894 (31.50%)	14,764 (36.04%)	13,299 (32.46%)	4 (0.01%)	
In terms of males (n=16,765)	2155 (12.85%)	6425 (38.30%)	8186 (48.83%)	4 (0.02%)	

Figure 2 illustrates the distribution of vitamin D levels across different seasons. Outliers falling outside the 2.5–97.5 percentile range were excluded from the analysis. Participants exhibited their highest 25(OH)D levels during the summer of both 2021 and 2022. In contrast, the lowest 25(OH)D levels were observed during the winter of 2022 and the spring of 2022.

A weak negative correlation was observed between age and 25(OH)D levels ($r=-0.038, P<0.001$) (Figure 3). Table 3 presents the distribution of 25(OH)D levels across age decades. Participants aged under one year exhibited the highest mean 25(OH)D level (34.9 ng/mL), while those aged between 20 and 29 years had the lowest mean 25(OH)D level (15.7 ng/mL).

Figure 2: The Distribution of 25(OH)D levels by season (2.5–97.5 percentile)

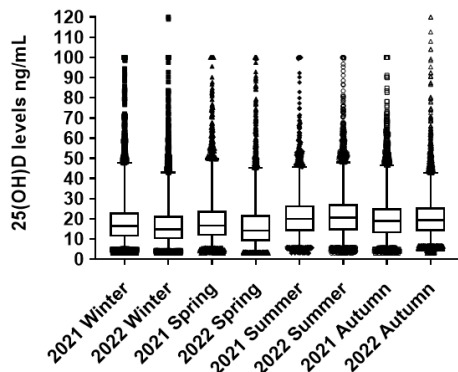


Figure 3: Correlation between age and 25(OH)D levels

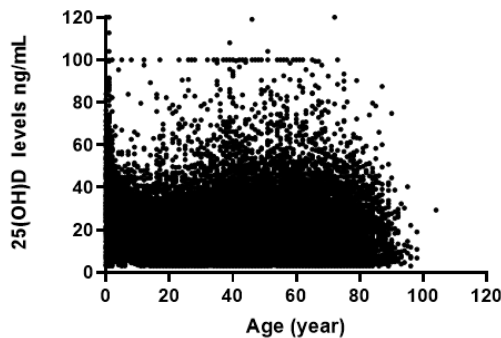


Table 3: 25(OH)D levels in terms of decades

25(OH)D level (ng/mL)	Age groups (years)									
	<1	1-9	10-19	20-29	30-39	40-49	50-59	60-69	≥70	
n	166	9679	7547	7456	7703	8968	7340	5120	3752	
Min-Max	3-120	3-120	3-100	3-100	3-108	3-119	3-104	3-100	3-120	
Mean	34.9	24.7	16.4	15.7	17.7	18.8	20.1	21.1	20.5	
SD	20.3	11.1	8.1	9.1	10.4	10.9	11.3	12.1	12.3	
Median	32.1	23.1	15.3	14.0	15.8	17.0	18.4	19.2	18.4	
Percent	0.3%	16.8%	13.1%	12.9%	13.3%	15.5%	12.7%	8.9%	6.5%	

Min: minimum, Max: Maximum

Discussion

The study investigated the distribution of 25(OH)D levels among residents of Niğde Province, which is located in proximity to both the Mediterranean and Central Anatolian regions. Additionally, the study assessed 25(OH)D levels in relation to the clinical decision points of the VDC, ES, and FNB.

Our results revealed a higher prevalence of vitamin D insufficiency and deficiency among female participants compared to their male counterparts. Furthermore, the findings demonstrated significant variations in vitamin D deficiency with respect to the clinical decision points of the VDC, ES, and FNB. Notably, this study represents the inaugural investigation into the distribution of 25(OH)D levels among residents of Niğde Province.

Vitamin D deficiency and insufficiency are prevalent on a global scale [9], and our findings align with previous studies conducted among both general and local populations [10-13]. However, a discrepancy arises when different clinical decision points are used to assess vitamin D status [14,15]. In our study, we adopted the clinical decision points established by the ES, but we also compared them to those specified by two other organizations. Our results revealed that a significant majority of participants (n=50,833; 88%) were classified as vitamin D deficient according to the VDC criteria, which define vitamin D insufficiency as levels below 30 ng/mL. Meanwhile, according to the ES criteria, more than half of the participants (n=36,256; 62.8%) fell into the vitamin D deficient category, with vitamin D

insufficiency defined as levels below 20 ng/mL. Lastly, based on the FNB criteria, over a quarter of the participants (n=15,049; 26.1%) were classified as vitamin D deficient, with vitamin D insufficiency defined as levels below 11 ng/mL. Remarkably, when categorized according to the criteria of these organizations, the number of participants with vitamin D insufficiency or optimal vitamin D levels appeared quite similar. Consequently, this discrepancy in vitamin D deficiency classification may pose diagnostic challenges.

Kader et al. [16] conducted a study in Karapınar, a neighboring settlement to Niğde province, where they reported two significant findings. First, they observed a higher prevalence of vitamin D deficiency and insufficiency among women compared to men. Second, they noted that older adults exhibited a higher incidence of vitamin D deficiency and insufficiency.

In a separate study conducted by Göktaş et al. [11] in the province of Bursa, Turkey, it was revealed that female participants had significantly lower vitamin D levels than their male counterparts. Additionally, they found that local residents had the highest vitamin D levels between March and May but the lowest levels between September and October.

Sezgin et al. [6] focused on vitamin D levels among the population residing in the Marmara region, documenting that three out of four people (75%) had vitamin D insufficiency (<20 ng/mL). Similarly, Hekimsoy et al. [12] conducted a cross-sectional study in the Aegean region and reported that three out of four individuals exhibited vitamin D insufficiency (74.9%) (<20 ng/mL).

In a study carried out by Vurmaz et al. [17] in Afyonkarahisar province, it was found that vitamin D insufficiency was more prevalent among women compared to men.

Finally, Solak et al. [18] conducted a large-scale study in Central Anatolia, reporting two significant findings. First, three out of four individuals had 25(OH)D levels below 20 ng/mL (76.25%). Secondly, women exhibited a lower mean of vitamin D levels.

We found that three out of five participants were vitamin D deficient (62.8%), according to the classifications of three different organizations. Additionally, our findings revealed that vitamin D deficiency was more common among female participants than male participants, a trend consistent with existing literature [6,11,12]. Research indicates that the prevalence of vitamin D insufficiency in Turkey ranges from 58.9% to 66.6%. Furthermore, studies have shown that newborns, pregnant women, and adult women are at an increased risk of vitamin D insufficiency. Alpdemir et al. [19] recommend that experts regularly monitor the 25(OH)D levels of Turkish individuals and encourage the use of vitamin D supplements when necessary.

In a large-scale study, Yeşiltepe-Mutlu et al. [13] assessed the effectiveness of the national vitamin D supplementation program in Turkey. They reported two significant findings. First, vitamin D deficiency was nearly eliminated in children under one year of age. Second, populations aged 11–18 years and 19–30 years had lower 25(OH)D levels than other groups, with levels below 20 ng/mL. Erol et al. [10] emphasized that vitamin D insufficiency is a

critical issue among Turkish children and adolescents. They also noted that vitamin D insufficiency persists from late winter through late summer despite vitamin D treatment. Andıran et al. [20] documented the widespread prevalence of vitamin D deficiency in Turkish female adolescents.

Our findings indicate that the national vitamin D program has effectively eradicated vitamin D deficiency in children under one year of age, with a mean 25(OH)D level of 34.9 ng/mL. However, our data reveals that one in four children aged 1–9 years exhibited an average 25(OH)D level of 24.6 ng/mL. Additionally, a notable decline in 25(OH)D levels during adolescence was observed, resulting in vitamin D insufficiency (25(OH)D levels <20 ng/mL). Specifically, our study highlights that individuals aged 20–29 years displayed the lowest 25(OH)D levels.

Turkey is situated between 36–42° north latitude and 26–45° east longitude. At higher latitudes, the solar zenith angle becomes very oblique between November and February, resulting in limited ultraviolet B (UVB) photon penetration to the Earth's surface. UVB radiation is crucial for synthesizing 25(OH)D [21,22]. In Turkey, the window for vitamin D synthesis falls between May and November. It is advisable for people in Turkey to spend time outdoors between 10:00 and 15:00 to optimize their vitamin D synthesis, as this is when the sunlight angle is most conducive [18].

Serum 25(OH)D levels are influenced by both dietary intake and sun exposure. Therefore, research findings suggest that deficiencies become more conspicuous as children grow older [21–23]. Our results affirm that advancing age accentuates vitamin D deficiency in adolescents and adults. Specifically, we observed the two lowest mean 25(OH)D levels in April 2022 (15.6 ng/mL) and February 2022 (16 ng/mL). Conversely, the two highest mean 25(OH)D levels were noted in July 2021 (22.7 ng/mL) and July 2022 (22.6 ng/mL).

Certain changes in 25(OH)D metabolism occur as individuals age, including a reduction in vitamin D receptor levels, renal 1.25(OH)₂D synthesis, and cutaneous 25(OH)D production [24]. Çağlayan et al. [25] and Şenyiğit et al. [26] have corroborated these findings, confirming a decline in 25(OH)D levels with increasing age. In our study, we identified a weak negative correlation between age and 25(OH)D levels. Our assessment of the geriatric population revealed a progressive increase in vitamin D insufficiency with advancing age.

Limitations

This study presents four notable limitations. First, we lack data regarding the duration of participants' sunlight exposure, their use of vitamin D supplements, their body mass index, and their choice of attire. Second, comprehensive information on parathyroid hormone, calcium, phosphorus, and magnesium levels was not available for all patients. Third, we did not possess data pertaining to rickets, osteomalacia status, or bone mineral density. Nevertheless, despite these limitations, the substantial dataset employed in this study allows for robust conclusions regarding the relationship between age, sex, and supplementation with 25(OH)D measurements.

Fourth, it's worth noting that the number of female participants significantly exceeded that of male patients, which may have implications for assessing vitamin D insufficiency.

Had there been a larger number of male participants, it is plausible that the average 25(OH)D levels might have been higher. Nonetheless, the relatively balanced gender distribution in our study remains an acceptable parameter for evaluating vitamin D insufficiency. Further investigations with a more even distribution of male and female participants are warranted to explore the underlying causes of vitamin D deficiency or insufficiency.

Conclusion

Our findings align with those of studies conducted in various regions of Turkey. Consequently, vitamin D deficiency appears to be a prevalent issue in Niğde province. Notably, the prevalence of vitamin D deficiency is higher among female participants compared to male participants. While the national vitamin D supplementation program appears to be beneficial for infants under one year of age, our data underscores that vitamin D levels decline with increasing age. Consequently, there is a need for the implementation of national supplementation programs targeting other age groups as well. We assert the importance of establishing population-based cutoff values to guide the development of comprehensive national vitamin D supplementation initiatives.

It is worth noting that although Turkey currently employs the clinical decision points of the ES for assessing vitamin D, variations in clinical decision points across different organizations may lead to discrepancies, particularly in diagnosing vitamin D deficiency. Therefore, fostering a consensus among organizations regarding vitamin D deficiency criteria could enhance the effectiveness of treatment strategies. We advocate for further research to corroborate our findings in future studies.

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