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Prevalence of Vitamin D Deficiency and Hypervitaminosis D Among Adult Patients Admitted to the Tertiary Care Hospitals in Turkey

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ABSTRACT

Objective: Vitamin D deficiency is a common health problem around the world. This study aimed to evaluate the nationwide prevalence of vitamin D status in tertiary care hospitals in Turkey.

Methods: Retrospectively, the data on vitamin D levels from 33 tertiary care hospitals' clinical biochemistry laboratories around Turkey between January and December were collected.

Results: In total, 706 434 serum samples from adult subjects (female/male: 469 028/237 406; 66.4%/33.6%) were included. While vitamin D levels were sufficient in 20.3% (n = 14 222), they were insufficient in 21.9% (n = 154 360) and deficient in 57.8% (n = 408 882).

We observed the highest rates of deficiency in those aged between 18 and 29 years (62.9%, n = 70 235) and lowest rates between 60 and 69 years (52.3%, n = 61 121) and between 70 and 79 years (52.3%, n = 32 397). Hypervitaminosis D was detected in 5.5% of adult subjects; highest rates of hypervitaminosis D were observed in those who were over 80 years (6.6%) and 70-79 years (6.5%) and the lowest in 18-29 years (2.8%).

Discussion: In this cohort, over half of the subjects admitted to the tertiary care hospitals in Turkey had vitamin D deficiency and required vitamin D supplementation. The elderly population had the lowest prevalence of vitamin D insufficiency and the highest prevalence of hypervitaminosis D.

Keywords: 25-Hydroxyvitamin D, vitamin D, vitamin D deficiency

Introduction

Vitamin D deficiency is a major public health problem worldwide in all age groups. Low serum vitamin D levels are associated with adverse clinical outcomes; therefore, identifying and treating deficiency may improve outcomes. The estimated prevalence of vitamin D levels below 20 ng/mL was previously reported as 37% in world,[1] 72% in China,[2] 26% in the United States,[3-5] 40% in Europe,[6] 37% in Canada.[7] In a meta-analysis from Turkey, vitamin D deficiency /insufficiency rates were found to be 63.5% among adults.[8] Vitamin D deficiency was found to be higher in specific groups, such as subjects from nursing homes,[9] long-term indoor healthcare workers,[10] and patients with obesity and diabetes.[11,12]

Vitamin D deficiency is related to chronic diseases, the tendency of some infections, and worsening of infections.[13] Treating vitamin D deficiency is cheap and may improve some clinical outcomes of chronic diseases and infections. Diagnosis and treatment of vitamin D deficiency and toxicity depend on laboratory measurements of 25(OH)D levels.[14] Vitamin D deficiency is relatively more common in hospital-admitted patients, and an inverse relationship between the frequency of vitamin D deficiency and hospital admission had been reported.[15] In Rai et al's study[16] and Amrein et al's study,[17] vitamin D deficiency was detected in 73.6% and 60.2% of tertiary care center-admitted patients, respectively, it was 71.23% among 6957 patients from a secondary care hospital laboratory,[8] and it was found to be 65.4% in a general hospital from India.[18]

Vitamin D levels vary seasonally, usually increasing from spring to summer and decreasing afterward. Aging, female gender, increased skin pigmentation, higher latitude, winter season, less sunlight exposure, topical application of sunscreen, dietary habits, and obesity are associated with lower 25(OH)D levels.[14,19,20] Also, in the study by Sezgin et al[21] the hospital-admitted patients affected by seasons' vitamin D levels were found to be higher in summer

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compared to winter.[21] In line with previous reports, in Amrein et al's study,[17] vitamin D deficiency was higher in winter compared to summer and autumn.

We hypothesize that the frequency of vitamin D deficiency in subjects who are admitted to hospitals is higher than in the general population, and vitamin D intoxication is also higher than reported. This study aimed to evaluate the nationwide prevalence of vitamin D status in tertiary care hospitals in Turkey. We determined age- and sex-related rates of vitamin D insufficiency, deficiency, and hypervitaminosis D in adult subjects admitted to tertiary care hospitals.

Material and Methods

Study Population and Study Locations

This nationwide study included 33 reference hospital laboratories, where vitamin D measurement is available in Turkey. In total, 21 biggest cities from south to north of country between 36° N and 42° N lattitudes with third-level reference hospitals were selected; [Adana (37° N), Ankara (39° N), Antalya (36° N), Aydın (37° N), Diyarbakır (37° N), Eskişehir (39° N), Erzurum (39° N), Giresun (40° N), İstanbul (41° N), İzmir (38° N), Kahramanmaraş (37° N), Kayseri (38° N), Kocaeli (40° N), Konya (37° N), Malatya (38° N), Mersin (36° N), Samsun (41° N), Tekirdağ (40° N), Trabzon (41° N), Yozgat (39° N), and Zonguldak (41° N)].

We collected the age of the participant on the date the sample was taken, sex, and vitamin D levels, retrospectively. Consecutive measurement of vitamin D levels in the tertiary care hospitals' clinical biochemistry laboratories around Turkey between January 2, 2016, and December 31, 2016, was recorded.

Data of age above 18 years with no additional exclusion criteria were included in the final analysis.

Thirty labs used chemiluminescence immunoassays (CLIA), and 3 labs used high-performance liquid chromatography (HPLC) for the measurement of serum 25(OH)D levels. The measurement range was 2-167 ng/mL for the CLIA method and 1.2-160 ng/mL for HPLC.

Marmara University Medical School Ethics Committee approved the study protocol (09.2017.519), and the data were conducted following the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki.

Study Design

Vitamin D deficiency was determined as a circulating 25(OH)D levels of less than 20 ng/mL (50 nmol/L), insufficiency as 20-29 ng/mL, and sufficiency as ≥30 ng/mL (75 nmol/L) according to the Endocrine Society Clinical Practice Guideline.[14] 25(OH)D levels less than 10 ng/mL was defined as severe vitamin D deficiency.[22] Hypervitaminosis D was defined as serum level of 25(OH)D > 50 ng/mL (125 nmol/L) and toxicosis as >100 ng/mL (250 nmol/L).[23,24] Subjects were divided into subgroups according to age, sex, and the season for vitamin D levels. The data were classified according to age (18-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, 70-79 years, and ≥80 years). Season classifications were winter (December, January, and February), spring (March, April, and May), summer (June, July, and August), and autumn (September, October, and November).

Statistical Analyses

Continuous variables were summarized using descriptive statistics presented as mean and standard deviation. Categorical variables were summarized using counts and percentages. Categorical data were analyzed using the chi-square (χ^2) test or Fisher's exact test appropriately. Mann–Whitney *U* and Kruskal–Wallis analysis of variance were used for comparing groups.

The results were evaluated at a 95% CI, and $P < .05$ was considered statistically significant. All statistical analyses were performed using software (Prism; GraphPad Software, Inc., San Diego, Calif, USA).

Results

In this study, 706 434 subjects' data were included and 66.4% (n = 469 028) of them were women. The distribution of 25(OH)D levels according to age groups, sex, and seasons is shown in Table 1.

25(OH)D Levels in the Whole Group

The median 25(OH)D level was 17.4 ng/mL (min-max: 0.1-945 ng/mL) in the whole group. The median 25(OH)D level was 16.6 ng/mL (min-max: 0.3-945 ng/mL) in women, and 18.3 ng/mL (min-max: 0.1-905 ng/mL) in men. There was no statistically significant difference in terms of vitamin D levels between men and women in the whole group ($P = .300$) (Table 1).

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Table 1. Median 25(OH)D Levels According to Gender, Age Groups, and Seasons Measured in Tertiary Hospital Laboratories from Turkey

	n (%)	25(OH)D Vitamin Levels, ng/mL, Median (Min-Max)	P
Whole group	706 434	17.4 (0.1-945)	
Sex			.300
Female	469 028 (66.4)	16.6 (0.3-945)	
Male	237 406 (33.6)	18.3 (0.1-905)	
25(OH)D vitamin levels, ng/mL			
<10	176 608 (25.0)		
10-19	232 274 (32.8)		
20-29	154 360 (21.9)		
30-49	104 573 (14.8)		
50-100	33 194 (4.7)		
100-149	4627 (0.7)		
≥150	828 (0.1)		
Age, years			**.001**
18-29	104 188 (14.7)	14.6 (0.8-945)	
30-39	114 936 (16.3)	15.8 (0.1-636)	
40-49	134 637 (19.1)	17.2 (0.1-606)	
50-59	146 583 (20.7)	18.4 (0.3-905)	
60-69	118 476 (16.8)	19.5 (0.3-623)	
70-79	62 754 (8.9)	19.4 (0.3-647)	
≥80	24 860 (3.5)	17.9 (0.3-288)	
Seasons			**<.001**
Winter (December, January, February)	166 420 (23.5)	15.0 (0.1-945)	
Spring (March, April, May)	194 120 (27.6)	15.2 (0.1-647)	
Summer (June, July, August)	160 336 (22.6)	19.3 (0.1-905)	
Autumn (September, October, November)	185 558 (26.3)	20.3 (0.1-623)	

Vitamin D deficiency was present in 57.8% (n = 408 852) of the whole subjects' blood samples measured for a year. Severe vitamin D deficiency (<10 ng/mL) was detected in 25% (n = 176 608) of the samples. 25(OH)D levels were over 50 ng/mL in 5.5% of the samples and 0.8% of samples (n = 5455) were over 100 ng/mL and were accepted as a toxic range (Table 1).

Vitamin D Levels According to Age

The lowest median 25(OH)D level was 14.6 ng/mL (min-max: 0.8-945 ng/mL) in subjects aged between 18 and 29 years. The highest median 25(OH)D levels were 19.5 ng/mL (min-max: 0.3-623 ng/mL) and 19.4 ng/mL (min-max: 0.3-647 ng/mL) in subjects in sixth decade and seventh decade, respectively . The lowest median vitamin D levels were observed in the twenties and thirties, which was statistically significant compared to the 60-69 and 70-79 years group ($P = .001$) (Table 1).

Although the highest vitamin D deficiency rates were observed in 18-29 years and 30-39 years, the prevalence of vitamin D deficiency ($P = .240$) and insufficiency ($P = .970$) was not statistically significant among the age groups (Table 2).

Vitamin D Levels in Men and Women

Median vitamin D levels were similar in men and women in the whole group (Table 1). The frequency of vitamin D deficiency was not different in women (59.2%) and men (55.4%) groups ($P = .660$).

Male subjects within the age group 18-29 years, 39-39 years, and over 80 years have higher vitamin D levels compared to the women group at the same age ($P < .001$, $P < .001$, $P = .010$, respectively) (Table 3).

The frequencies of vitamin D deficiency and insufficiency according to gender are shown in Table 4. The frequency of deficiency was higher both in the female and male groups than in the insufficiency ($P < .001$) and sufficient groups ($P < .001$).

Vitamin D Levels and Deficiency According to Seasons

Mean vitamin D levels were 23.6 ± 17.3 ng/mL for autumn, 23.3 ± 18.0 ng/mL for summer, 19.6 ± 18.5 ng/mL for winter, and 20.0 ± 18.6 ng/mL for spring.

Median vitamin D levels were higher in autumn and summer serum samples compared to winter and spring serum samples ($P < .001$) (Table 1). The frequency of vitamin D deficiency was higher in January, February, March, and April compared to June, July, August, September, and October ($P = .005$) (Figure 1), while the frequency of vitamin D deficiency was the highest in February (71.6%) and lowest in September with a 44.2% ratio.

Table 2. 25(OH)D Levels According to Age Groups

25(OH)D Levels	18-29 Years, n = 103 491	30-39 Years n = 114 025	40-49 Years n = 133 453	50-59 Years n = 145 000	60-69 Years n = 116 955	70-79 Years n = 61 927	≥80 Years n = 24 424	P
<20 ng/mL, n (%)	70 235 (67.9)	72 375 (63.5)	79 211 (59.3)	79 942 (55.1)	61 121 (52.3)	32 397 (52.3)	13 571 (55.5)	.240
20-29 ng/mL, n (%)	19 675 (19.0)	23 461 (20.6)	31 045 (23.3)	33 785 (23.3)	27 816 (23.8)	13 851 (22.4)	4727 (19.4)	.970
30-49 ng/mL, n (%)	10 667 (10.3)	14 078 (12.3)	18 641 (14.0)	23 801 (16.4)	21 245 (18.1)	11 634 (18.8)	4507 (18.5)	.430
≥50 ng/mL, n (%)	3611 2.8	5022 3.6	5740 3.4	9055 5.2	8294 5.8	4872 6.5	2055 6.6	.600

P values were given for each line.

Table 3. Mean 25(OH)D Levels According to Age Groups and Gender

Age	Women n = 469 028	Men n = 237 406	25(OH)D Levels		*P*
			Women	Men	
18-29	69 863 (14.9)	34 325 (14.5)	17.2 ± 16.3	20.3 ± 15.6	**<.001**
30-39	78 137 (16.6)	36 799 (15.5)	19.5 ± 17.2	21.5 ± 15.2	**<.001**
40-49	91 717 (19.5)	42 920 (18.1)	21.3 ± 18.6	21.6 ± 17.5	.430
50-59	98 365 (20.9)	48 218 (20.3)	23.3 ± 19.0	22.3 ± 16.7	.070
60-69	76 084 (16.2)	42 392 (17.8)	23.6 ± 21.0	23.4 ± 17.1	.260
70-79	39 212 (8.6)	23 542 (9.9)	24.5 ± 21.2	23.1 ± 18.0	.320
≥80	15 650 (3.3)	9210 (3.9)	21.1 ± 22.2	22.5 ± 20.2	**.010**

Values reported as n (%) and mean ± standard deviation. The numbers in bold indicate the statistical significance ($P < .05$).

Table 4. Vitamin D Status According to Gender and Seasons

	Deficiency (≤20 ng/mL)	Insufficiency (20-30 ng/mL)	Sufficiency (≥30 ng/mL)	*P*
Total	408 852 (57.9)	162 363 (23.0)	135 219 (19.1)	**<.001**
Female	277 384 (59.2)	101 542 (21.6)	90 102 (19.2)	**<.001***
Male	131 468 (55.4)	60 821 (25.6)	45 117 (19.0)	**<.001***
Age				
Female	47.03 ± 16.7	50.21 ± 16.8	52.9 ± 16.3	.730
Male	49.14 ± 17.2	50.05 ± 16.6	52.4 ± 16.1	
Frequency according to seasons				
Winter	106 974 (63.5)	32 607 (19.4)	28 843 (17.1)	**<.001**
Spring	128 163 (63.8)	36 521 (18.2)	36 178 (18.0)	**<.001**
Summer	84 603 (54.3)	42 631 (27.3)	28701 (18.4)	**<.001**
Autumn	89 112 (49.2)	50 604 (27.9)	41497 (22.9)	**<.001**

Values reported as n (%) and mean ± standard deviation.
*P values were given for each line. The numbers in bold indicate the statistical significance ($P < .05$).

Discussion

Our study is in line with previous reports that vitamin D insufficiency and deficiency are common in the tertiary care hospital-admitted subjects, which affected 57.8% of our cohort. Severe vitamin D deficiency was observed in 25% and toxic levels in 0.8% of the cohort. While the highest vitamin D levels were detected in subjects aged between 60 and 79 years, the frequency of vitamin D deficiency was similar between the age groups. Median 25(OH) levels and vitamin D deficiency frequencies were similar between women and men in the whole group. Median 25(OH)D levels in summer and autumn were higher than in spring and winter in the whole cohort. To date, this is the largest study of vitamin D status among hospital-admitted patients in Turkey.

The levels of vitamin D below 30 ng/mL have been reported in a wide range of distribution, ranging between 26.4% and 77.7% in the literature.[14,25-28] While in Korea National Health and Nutrition Examination Survey, 65.7% of males and 76.7% of females had deficient vitamin D levels,[29] it was detected in 55.4% and 59.2% of males and females, respectively, in our study. Delos Reyes et al's[28] study which included 15 708 subjects admitted to tertiary care hospitals reported that the vitamin D deficiency rate was 11.2%, insufficiency was 32.4%, and sufficiency was 56.4%. Vitamin D deficiency was detected in 73.6% and 60.2% of tertiary care center-hospitalized patients.[16,17] While severe deficiency was reported as 26.9%,[30] 20.8%,[31] 11.2%[28] in previous reports, it was 25% in our study. In our

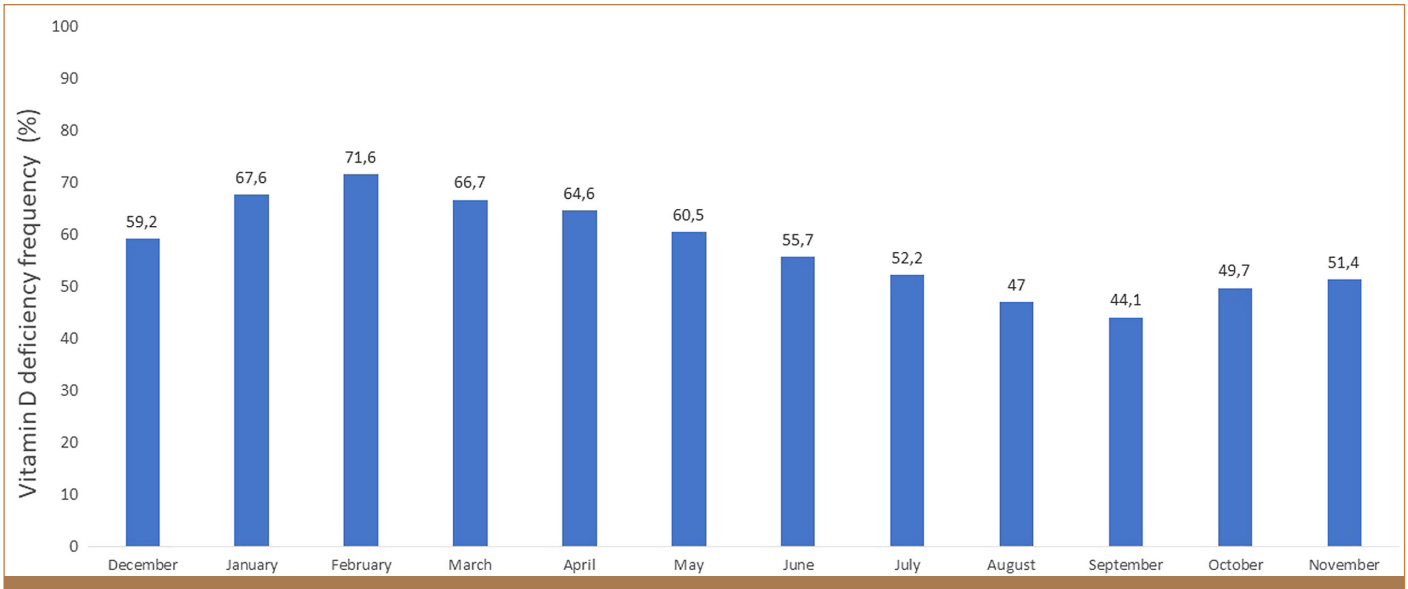


Figure 1. The frequency of vitamin D deficiency in the whole group according to months.

study, sufficient vitamin D levels were detected in 20.3% of patients, while it ranged between 2.7% and 56.4% in the literature.[28,31]

Similar to previous reports,[28,29,31] in our study, 25(OH)D levels were higher in older subjects compared to subjects aged below 30 years. Vitamin D deficiency in the young adult group is related to decreased outdoor activities and aggressive sun protection.[14] We attribute the higher levels of 25(OH)D in the elderly population in this cohort due to the possible supplementation of vitamin D in this group.

In Forrest et al's[19] study, which evaluated data from 2005 to 2006 of NHANES, the subjects aged between 55-59 and 60-64 had the highest prevalence rate of vitamin D deficiency. On the other side, in Basile et al's[26] study, subjects aged ≤45 years or 46-64 years had higher vitamin D levels compared to those older than 65 years.

There are controversial results about the effect of gender on vitamin D deficiency. Similar to Forrest et al's[19] study,[19] we found that vitamin D levels were similar both in men and women. In studies by Yu et al[31] and Muscogiuri et al[12] women had lower vitamin D levels than men. In Hilger et al's[1] study, 25(OH)D levels in women tended to be lower, especially in the Asia/Pacific and Middle East/Africa regions. Contrary to this, in studies by Basile et al[26] and Delos Reyes et al[28] vitamin D levels were significantly higher in women than in men.

In line with previous reports, the median 25(OH)D levels varied significantly according to the seasons, and deficiency was found to be most prevalent in spring and winter compared to other seasons.[5,14,30-33]

The 25(OH)D results of the hospital-admitted patients may not be completely compatible with the healthy population. As the study is retrospective, the dietary habits of patients, food fortifications, taking vitamin D supplements, or duration of sun exposure are not known. Lastly, 2 different methodologies for 25(OH)D measurements were used, CLIA and HPLC. The most valid method has been reported as HPLC, and measurements with CLIA could result in lower values.[34]

Conclusion

The overall prevalence of vitamin D deficiency in hospital-admitted subjects is similar to those in hospital-derived studies from National Turkish and European populations. In this cohort, over half of the subjects admitted to the general hospitals in Turkey had vitamin D deficiency requiring vitamin D supplementation. Although this retrospective study was not able to exclude vitamin D-related diseases and vitamin D-treated patients, the highest prevalence of hypervitaminosis D is observed in the elderly population which may indicate overtreatment of vitamin D supplementation in the tertiary care hospitals in Turkey. Further prospective studies are needed to guide appropriate vitamin D supplementation for subgroups and to prevent overtreatment.

Ethics Committee Approval: The study was approved by the medical ethics committee of Marmara University Medical School (No: 09.2017.519).

Informed Consent: N/A.

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Declaration of Interests: The authors declare that they have no conflict of interest.

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