ISSN 2458-8865 E-ISSN 2459-1505
www.fppc.com.tr
Family Practice & Palliative Care

Research Article

Evaluation of the response given to the vitamin D treatment in patients with osteomalacia

Osteomalazili hastalarda vitamin D tedavisine verilen cevabın değerlendirilmesi

Selin Genc[a], Omer Genc[b], Mehmet Fatih Kilicli[c]

[a] Department of Endocrinology, Faculty of Medicine, Malatya Inonu University, Malatya, Türkiye
[b] Department of Internal Medicine, Malatya Training and Research Hospital, Malatya, Türkiye
[c] Department of Endocrinology, Medipol University Medical School, Istanbul, Türkiye

Abstract

Introduction: The current study aimed to examine the relationship between 25 hydroxyvitamin D [25(OH)D] levels and demographic, clinical and laboratory parameters and response to treatment in patients living in a Central Anatolian city of Turkey and diagnosed with osteomalacia.

Methods: A total of 533 patients who live in the continental climate, older than 18 years old, and have 25(OH)D levels lower than 30 ng/ml were enrolled prospectively. Patients' age, body mass index (BMI), type of clothing, season in which they were diagnosed, type of treatment and duration were recorded. At the time of diagnosis, the patients were evaluated with clinical and laboratory parameters at 1st, 2nd, and 4th months.

Results: Mean serum 25(OH)D level was 7.59±4.41 ng/mL at the time of diagnosis. 25(OH)D level was 24.42±14.77 ng/ml after treatment, with severe deficiency (<10 ng/mL) in 74% of patients, deficiency (<20 ng/mL) in 24.2%, insufficiency in 1.3% (20-29.99 ng/mL). 74.4% of the women had a closed clothing style. Vitamin D levels during diagnosis and at the end of treatment did not differ according to the BMI and the diagnosis period (p> 0.05). However, as BMI increased, the response given to the treatment decreased.

Conclusions: The current study showed that vitamin D deficiency is common in study population. The current findings demonstrate that treatment and follow-up should be continued until achieving normal serum 25(OH)D levels, taking into account geographic and ethnical structures to bring vitamin D levels to adequate levels.

Keywords: 25-hydroxytamin D; Osteomalacia; vitamin D deficiency

Öz

Giriş: Bu çalışmada Türkiye'nin bir Orta Anadolu kentinde yaşayan, osteomalazi tanısı alan hastalarda 25 hidroksivitamin D [25(OH)D] düzeylerinin demografik, klinik ve laboratuvar parametreleriyle olan ilişkisi ve tedaviye yanıtının incelenmesi amaçlandı.

Yöntem: Karasal iklimdeki şehirde, 25(OH)D <30 ng/ml, > 18 yaşından büyük olan 533 hasta prospektif olarak dahil edildi. Hastaların yaşı, vücut kitle indeksi (VKİ), giyim şekli, tanı aldığı mevsim, tedavi şekli ve süresi kaydedildi. Hastalar tanı anında, 1., 2. ve 4. aylarda klinik ve laboratuvar parametreleri ile değerlendirildi.

Bulgular: Tanı anında ortalama serum 25(OH)D 7,59±4,41 ng/mL idi. Hastaların %74'ünde ciddi eksiklik (<10), %24,2'sinde eksiklik (<20), %1,3'ünde yetersizlik (20-29,99) olup tedavi sonrası 25(OH)D: 24,42±14,77 ng/ml idi. Kadınların %74,4'ü kapalı giyim tarzına sahipti. Tanı sırasında ve tedavi sonunda Vitamin D düzeyleri, BKİ ve tanı mevsimine göre farklılık göstermedi (p>0,05). Ancak VKİ arttıkça tedaviye verilen cevabın azaldığı bulundu.

Sonuç: Bu çalışma, bölgemizde vitamin D eksikliğinin yaygın olarak görüldüğünü ortaya koymuştur. Bulgularımız D vitamini düzeyini yeterli seviyeye çıkarmak için coğrafik ve etnik yapıların da göz önünde bulundurularak, normal serum 25(OH)D düzeyine ulaşıncaya kadar tedavi ve takibe devam edilmesi gerektiğini göstermektedir.

Anahtar Kelimeler: 25-hidroksivitamin D; osteomalazi, vitamin D yetersizliği

Received	Accepted	Published Online	Corresponding Author	E-mail
June 7, 2022	September 6, 2022	December 30, 2022	Selin Dincer Genc, M.D.	nilesenay@hotmail.com
Correspondence	Dr. Selin Genc. Inonu University, Faculty of Medicine, Department of Endocrinology and Metabolism,44100 Malatya, Türkiye			
doi	https://doi.org/10.22391/fppc.1127577			

Key Points

1. Vitamin D level is affected by your geography and climate condition.
2. Clothing style, seasonal changes, body mass index are effective factors in vitamin D treatment.
3. Classic laboratory findings may not always be present in osteomalacia.

Introduction

Vitamin D is a fat-soluble prohormone that plays an important role in bone health. Vitamin D is synthesized from the precursors found in the skin as a result of exposure to ultraviolet rays. Vitamin D synthesis in the skin is affected by many factors such as season, direct contact with the sun, angle of incidence of sun rays, sun exposure time, geographical location, amount of melanin in the skin, use of sunscreen, age, gender, pregnancy, clothing style and obesity [1].

The major circulating form used in the determination of vitamin D level is 25(OH)D vitamin, and it reflects all vitamin D sources of the body as it originates from both endogenous and exogenous sourced vitamin D. While most of the vitamin D in serum is in the form of 25(OH)D, only a small part is found in the form of its active metabolite, 1,25(OH)2D. Vitamin D produced in the skin is metabolized to 25(OH)D more rapidly than dietary intake. Although 1,25(OH)D levels increase even with short-term sun exposure, 25(OH)D levels are almost not affected. For these reasons, measurement of total 25(OH)D levels is the most used method to see the status of vitamin D stores. 1,25(OH)2D increases intestinal calcium and phosphate absorption, hypocalcemia and hypophosphatemia that may occur in case of deficiency of vitamin D and its metabolites [2,3].

Osteomalacia is a metabolic bone disease characterized by impaired mineralization of the bone as a result of a deficiency in vitamin D or a problem in its metabolism. Since musculoskeletal symptoms such as local or widespread bone pain, muscle pain, and weakness can be seen in osteomalacia; It can occur with a clinic that mimics many diseases such as osteoporosis, fibromyalgia, polymyalgia rheumatica, rheumatoid arthritis, diffuse idiopathic skeletal hyperostosis, multiple myeloma, and metastatic bone disease [4,5]. Vitamin D deficiency is an issue that needs to be considered because it increases the risk of bone fracture, causes morbidity and increases health expenditures [6].

While the importance of vitamin D deficiency has been revealed by various studies all over the world, there are still debates about its treatment. Discussions about the criteria for giving treatment, the dose and duration of treatment continue. In this study, in patients diagnosed with osteomalacia and living in Sivas, the central Anatolian city of Turkey, vitamin D levels were determined by the season, gender, age, body mass index (BMI) and clothing style. In addition, we aimed to find clues about the effectiveness of the treatment, the dose and duration of the treatment in our patient group by examining the responses of the patients who were given vitamin D therapy in a multifaceted way.

Methods

Study Design

The cross-sectional descriptive study. The Cumhuriyet University Clinical Research Ethics Committee approved the current study protocol. The patients participating in the study were informed about the study and their informed consent was obtained.

Location

Sivas Province is a large region with a population of 623,535 at 37:02 and 39:45 latitude-longitude. It has a continental climate with long, rainy and cold winters and hot and short summers. Average daylight is 2.4 hours/day in winter and 12.1 hours in summer. Traditionally, women prefer closed clothes, except for the face and hands.

Patients

533 patients aged 18-86 years (mean 43.98 ± 14.95 years) who applied to the Endocrinology and Metabolic Diseases Department of the Cumhuriyet University Medical Faculty Hospital between January 2010 and July 2011 were diagnosed with primary osteomalacia after clinical inquiries and examinations were included in the study. The diagnosis of osteomalacia was made when vitamin D3 deficiency was accompanied by at least one of the clinical findings (Bone pain and muscle weakness, Bone sensitivity, fracture, Difficulty walking and duck-like gait, Muscle spasms or cramps and positive Chvostek sign).

The patients were divided into groups according to their vitamin D levels and their treatment was planned. They were called for follow-up in the 1st, 2nd and 4th months after the treatment. Patients who reached the target vitamin D level were excluded from follow-up. Those with liver disease, renal failure, hyper or hypoparathyroidism, those taking calcium and vitamin D, and those with endocrine, renal or hepatic disease affecting vitamin D metabolism were not included in the study.

Data collection

Patients' gender, height (cm), body weight (kg), BMI (kg/m²) (18.5-24.9 healthy/25-29.9 overweight/30-34.9 obese/35-39.9 extremely obese/>40 morbidly obese), the season in which the patients were diagnosed was recorded because of the seasonal variation in vitamin D levels.
In order to evaluate the relationship of the laboratory parameters examined in the study with age, the patients were divided into groups according to certain age ranges (15-29 years, 30-49 years, 50-69 years, >70 years).

The way of dressing of female individuals was questioned as “Dressing to expose only the face and hands: YES / NO”.
Venous blood samples were taken from the patients to biochemistry tubes between 08:00 and 09:00 in the morning following a 12-hour fast. Serum was separated by centrifugation at 5000 rpm for 10 minutes.

25(OH)D and Parathormone (PTH) were studied by electrochemiluminescence immunoassay (ECLIA) method on Roche-HITACHI device (Cobas E 601 model). Serum Vitamin D3 level (>30 target value/20-29.99 insufficiency /10-19.99 deficiency/<10 severe deficiency was accepted as
Serum calcium (mg/dL) by ion-selective method, serum phosphorus (mg/dL) by colorimetric/phosphomolybdate-UV method, serum alkaline phosphatase (IU/L) by kinetic rate method, serum creatinine (mg/dL) by colorimetric/alkaline picrate method, serum albumin (g/dL) colorimetric/BCP method was studied on Beckman Coulter LX 20 autoanalyzer device using Synchron commercial kit. The normal value ranges

in the serum according to the recommendations of the manufacturers are: Calcium (8.4-10.5 mg/dl), phosphorus (2.4-4.5 mg/dl), alkaline phosphatase (38-126 IU/L), parathyroid hormone (15-65 pg/ml), albumin (3.5-5 g/dl) 17), creatinine (0.4-1.0 mg/dl).

Follow-up with Vitamin D Status and Laboratory Values

According to the vitamin D levels measured at the time of diagnosis and during the follow-ups, 300,000 IU oral vitamin D3 treatments were given to patients with severe deficiency once a week, once every 2 weeks for patients with deficiency, and once a month for patients with insufficiency. Patients were called for follow-up at 1st , 2nd and 4th months. Patients who reached the target value (>30) were excluded from treatment and follow-up. After the treatment, 25(OH)D levels, clinical symptoms, satisfaction with their health, serum biochemistry and hormone parameters were re-examined.

Ethical approval, informed consent and permissions

The study protocol was approved by the Ethics Committee of Cumhuriyet University (date: 10.02.2010, Approval number: 2010/1-2). A written informed consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

The data of our study were analyzed using the SPSS for Windows (SPSS Inc., Chicago, IL, USA, version 14.0) program. Descriptive statistics were shown as mean, standard deviation, for continuous variables, and frequency (n) and percentage (%) for categorical variables. Normality distribution of numerical data was evaluated with Kolmogorov-Smirnov test. We used Student t test for comparison of two independent groups. For comparison of more than two independent groups, we used the One Way Anova test for normally distributed continuous data. Analysis of variance and Tukey correction test were used. p<0.05 was considered statistically significant.

Results

A total of 533 (65 males, 468 females) individuals with a 25(OHD) level below the target value (<30 ng/ml) were included in the study. According to the vitamin D levels measured at the time of diagnosis, 74.5% (n=397) of the patients were severely deficient, 24.2% (n=129) were deficient, and 1.3% (n=7) were insufficient. Among these patients, who were called for control by giving vitamin D treatment, 529 patients came to the first follow-up, 323 patients to the second follow-up, and 177 patients to the third follow-up. The distribution of patients in groups was determined according to the season in which the patients were diagnosed, age groups, vitamin D levels before the treatment and after the follow-up at the 4th month, and the way of dressing of the female patients are given in **Table 1.**

Table 1. The distribution of the individuals was included in the study according to the seasons they were diagnosed with, age, clothing style of female individuals, and Vit-D3 Level after diagnosis and treatment

Variables	n (%)	n (%)	n (%)	n (%)	Total n (%)
Seasons	**Spring n (%)**	**Summer n (%)**	**Autumn n (%)**	**Winter n (%)**	
	322 (60.4)	64 (12.0)	57 (10.7)	90 (16.9)	533 (100.0)
Age(years)	**18-29 years**	**30-49 years**	**50-69 years**	**≥ 70 years**	
	108(%20.3)	222(%41.7)	181 (%34.0)	22 (%4.1)	533 (100.0)
Vit-D3 (ng/ml)	**Normal**	**insufficiency**	**deficiency**	**Serious deficiency**	
During Diagnosis	0 (0.0)	7 (1.3)	129 (24.2)	397 (74.0)	533 (100.0)
Post treatment	218 (40.9)	115 (21.6)	124 (23.3)	76 (14.3)	533 (100.0)
Covered clothes	Yes	No			468 (100.0)
	348 (74.4)	120 (25.6)			

Covered clothes= Dressing to Expose Only the Face and Hands; VitD3: vitamin D3; **Normal:** Vit-D3 level>30 ng/ml; **insufficiency**: Vit-D3 level=20-29.9 ng/ml; **deficiency**: Vit-D3 level=10-19.9 ng/ml; **serious deficiency**: Vit-D3 level<10 ng/ml

While the mean serum 25(OH)D level of all individuals before the treatment was 7.59±4.41 ng/ml, it was 24.42±14.77 ng/ml in the 1st month after the treatment. In the first follow-up of the patients in the first month after the treatment, 218 (49%) reached the target value, 115 (21.6%) were found to have insufficiency, 124 (23.3%) had a deficiency, and 76 (14.3%) had serious deficiency. 218 patients who reached the target value were excluded from follow-up. While 147 (45.5%) of the 315/323 patients whose treatment was continued reached the target value in the 2nd month follow-up, insufficiency was detected in 84 (26%), deficiency in 74 (22.9%), and serious deficiency in 18 (5.6%) patients. At the 4th month follow-up, 102 (57.6%) of the patients reached the target value, 45 patients (25.4%) had insufficiency, 26 (14.7%) had a deficiency, and 4 (2.3%) had severe deficiency. Vitamin D levels at the time of diagnosis were compared according to the seasons, and although the vitamin D level was highest in autumn (9.03±4.46 ng/ml), the difference between seasons was found to be statistically insignificant (p>0.05, Table 2).

The distribution of the mean vitamin D levels of the patients by age groups at the time of diagnosis: 15-29 years: 6.34±3.84 ng/ml, 30-49 years: 7.85±4.06 ng/ml, 50-69 years: 8.44±5.95 ng/ml, with age A significant correlation was found between vitamin D levels (p < 0.05). When the vitamin D values in different age groups were compared in pairs, the difference between the 18-29 and 30-49 age groups and between the 18-29 age group and the 50-69 age group was significant (p<0.05), while the difference between the other age groups was insignificant (p> 0.05). When the vitamin D values of the individuals at the beginning of the treatment were compared according to gender, the difference was found to be significant (p<0.05). At the time of diagnosis, 25(OH)D deficiency was found to be 87.8% in women and 12.2% in men (p<0.05). The mean vitamin D level of male patients was higher than that of females. However, the difference between the male and female individuals according to the treatment outcome was insignificant (p>0.05).

Table 2. Comparison of treatment outcome according to treatment type

Treatment type	Vitamin D Level by Treatment Result (ng/ml)				
Treatment after diagnosis	**Normal**	**Insufficiency**	**Deficiency**	**Serious deficiency**	**Total**
	n (%)	n (%)	n (%)	n (%)	n (%)
Once a week	108 (56.8)	32 (16.8)	29 (15.3)	21 (11.1)	190 (100.0)
Biweekly	27 (32.1)	19 (22.6)	22 (26.2)	16 (19.0)	84 (100.0)
Every Three Weeks	75 (37.3)	55 (27.4)	53 (26.4)	18 (9.0)	201 (100.0)
Once in a month	7 (13.0)	7 (13.0)	19 (35.2)	21 (38.9)	54 (100.0)
Second control					
Once a week	3 (25.0)	3 (25.0)	4 (33.3)	2 (16.7)	12 (100.0)
Biweekly	35 (61.4)	12 (21.1)	8 (14.0)	2 (3.5)	57 (100.0)
Every Three Weeks	93 (47.4)	58 (29.6)	39 (19.9)	6 (3.1)	196 (100.0)
Once in a month	16 (27.6)	11 (19.0)	23 (39.7)	8 (13.8)	58 (100.0)
Third control					
Once a week	5 (71.4)	0 (.0)	2 (28.6)	0 (.0)	7 (100.0)
Biweekly	13 (54.2)	6 (25.0)	4 (16.7)	1 (4.2)	24 (100.0)
Every Three Weeks	60 (59.4)	30 (29.7)	10 (9.9)	1 (1.0)	101 (100.0)
Once in a month	24 (53.3)	9 (20.0)	10 (22.2)	2 (4.4)	45 (100.0)

VitD3: vitamin D3; Normal: Vit-D3 level>30 ng/ml; insufficiency: Vit-D3 level=20-29.9 ng/ml; deficiency: Vit-D3 level=10-19.9 ng/ml; serious deficiency: Vit-D3 level<10 ng/ml

When the ALP, PTH, VitD3, creatinine values at the beginning of the treatment were compared according to the gender of the individuals, the difference was found to be significant (p<0.05), while the difference was found to be insignificant when the Ca, P, albumin values were compared. (p>0.05). According to this report, men's ALP, creatine, and VitD3 values were found to be higher than women's, while women's PTH values were also higher than men's **(Table 3).**

Table 3. Comparison of measured parameters at diagnosis by age groups and gender

	Ca mean±SD	**P** mean±SD	**ALP** mean±SD	**PTH** mean±SD	**Vit-D3** mean±SD	**Albumin** mean±SD	**Creatinine** mean±SD
Age groups							
15-29 years	9.31± 0.95	3.29±0.62	66.73± 39.14	46.63± 25.81	6.34± 3.84	4.40 ±0.39	0.71± 0.17
30-49 years	9.19± 0.48	3.24±0.78	63.15± 21.56	52.22± 26.15	7.85 ±4.06	4.08 ±0.32	0.70 ±0.14
50-69 years	9.26± 0.58	3.32±0.58	71.59±24.94	57.11± 32.47	8.44 ±5.95	3.96 ±0.51	0.74 ±0.17
≥70 years	9.19 ±0.51	3.70 ±0.59	78.34±26.64	63.58± 40.55	6.52 ±3.36	3.98 ±0.33	0.92 ±0.30
p value	F=0.86 p=0.457	F=2.50 p=0.059	***F=3.05 p=0.028***	***F=2.98 p=0.031***	***F=4.93 p=0.002***	***F=11.11 p=0.001***	***F=8.84 p=0.001***
Gender							
Male	9.16 ±1.56	3.14 ±0.63	76.50 ±24.48	44.93 ±17.56	9.46± 6.62	4.15± 0.44	0.88 ±0.20
Female	9.25± 0.52	3.32± 0.69	66.11± 28.03	54.50 ±30.59	7.44 ±4.42	4.11 ±0.44	0.70± 0.16
p value	t=0.99 p=0.321	t=1.79 p=0.073	***t=2.40 p=0.017***	***t=2.13 p=0.033***	***t=3.22 p=0.001***	t=0.53 p=0.593	***t=7.36 p=0.001***

F= One Way Anova Test; t: Independent samples t-test; SD: standard deviation; Ca: calcium; P: phosphate; ALP: alkaline phosphatase; PTH: parathyroid hormone; VitD3: vitamin D3

Closed clothing was present in 74.4% of 468 female patients in whom we found vitamin D deficiency. When the vitamin D levels of female patients were compared according to the way of dressing, no significant difference was found (p>0.05).

When the vitamin D level measured at the time of diagnosis and BMI were compared, the difference was insignificant (p>0.05). When the vitamin D levels after treatment were examined, a significant relationship was found when the other groups were compared with those who reached the target value (>30ng/ml). Since vitamin D is stored in fat, the response to treatment decreases as BMI increases.

When the PTH values of the individuals at the beginning of the treatment were compared according to BMI, the difference was found to be significant (p<0.05). When the PTH values of BMI were compared in pairs, the difference between healthy and morbidly obese and between overweight and morbidly obese was significant, while the difference between other groups was insignificant (p>0.05). According to this report, the PTH value of the morbidly obese was higher than that of the healthy and overweight.

When the albumin values of the individuals at the beginning of the treatment were compared according to BMI, the difference was found to be significant (p<0.05). When the Albumin values of BMI were compared in pairs, the difference between healthy and severely obese and between healthy and morbidly obese was significant (p<0.05), while the difference between other groups was insignificant (p>0.05). As can be seen, the albumin values of severely obese and morbidly obese are lower than healthy individuals. The higher the BMI, the lower the albumin value.

When the Ca, P, ALP, VitD3, creatine values of the individuals at the beginning of the treatment were compared according to BMI, the difference was found to be insignificant (p>0.05).

There is a positive correlation (r=0.174) between PTH and ALP at the time of diagnosis. As the PTH value increases, the ALP value also increases. Although this correlation coefficient is statistically significant, it is weak as a correlation criterion.

No significant relationship was found between BMI and vitamin D, Ca, P, ALP and creatinine. The PTH value in obese patients participating in the study was found to be higher than healthy and overweight patients. However, patients with higher BMI after treatment had lower vitamin D levels. **(Table 4).**

Table 4. Comparison of Parameters Measured at the Time of Diagnosis of Individuals According to BMI Status

	Healthy mean±SD	Overweight mean±SD	Slightly Obese mean±SD	Severely obese mean±SD	Morbid obese mean±SD	p value
Ca (mg/dl)	9.28 ±0.84	9.30 ±0.42	9.17± 0.70	9.17± 0.44	9.18 ±0.43	F=0.301 p=0.303
P (mg/dl)	3.31± 0.82	3.25± 0.60	3.28± 0.58	3.36 ±0.75	3.47± 0.43	F=0.493 p=0.741
ALP (Iu/L)	66.91± 25.77	67.98 ±31.09	73.00 ±25.79	66.27 ±26.75	69.76 ±26.18	F=1.592 p=0.175
PTH (pg/ml)	49.26 ±27.42	51.53± 23.79	58.81 ±39.74	53.15 ±23.76	72.19 ±21.85	***F=2.831 p=0.024***
VitD3 (ng/ml)	7.27 ±5.33	8.12 ±4.69	7.99± 4.48	6.98± 3.87	7.49 ±4.97	F=1.094 p=0.356
Albumin (g/dl)	4.30± 0.42	4.08± 0.53	4.13 ±0.30	3.89 ±0.32	3.81 ±0.14	***F=5.742 p=0.001***
Creatinine (mg/dl)	0.72± 0.18	0.72± 0.16	0.74 ±0.19	0.73± 0.17	0.72 ±0.12	F=0.303 p=0.877

Healthy: BMI= 18.0-24.9; Overweight: BMI=25-29.9; Slightly Obese: BMI=30-34.9; Severely Obese: BMI=35-39.9; Morbid Obese: BMI≥40; F= One Way Anova Test; t: Independent samples t-test; SD: standard deviation; Ca: calcium; P: phosphate; ALP: alkaline phosphatase; PTH: parathyroid hormone; VitD3: vitamin D3

Discussion

Vitamin D deficiency is a worldwide health problem [1,5]. According to the main results of our study; There was no difference in vitamin D levels among women with different dressing styles, there was no difference in vitamin D levels of patients diagnosed in different seasons, while serum vitamin D levels reached target values in most of the patients with oral vitamin D therapy, the patients treated were generally satisfied with their health and muscle mass.

Response to vitamin D treatment did not differ between patients of different genders, age groups, and dressing styles. There are limited number of studies on this subject in our country [7-10]. As far as we know, there is not yet a study with a large number of patients examining the relationship between vitamin D deficiency and laboratory parameters and evaluating the response to treatment in a population with a continental climate and typical Anatolian clothing style. This study is the first study in this direction.

Holick et al. showed that geographic location, season, and sunshine hours are also important in vitamin D synthesis [4]. In the Sivas region, where the study was conducted, a continental climate prevails generally cold, with long winters and hotter but short summers. Patients were included in the study in all seasons, including spring, summer, autumn and winter. The dressing styles of women living in Sivas are generally covered by traditional clothes, leaving only the face and hands exposed.

It is thought that a calcidiol level above 30 ng/ml is necessary for optimal bone health and protection from many health problems (6). While a calcidiol level above 30 ng/ml increases calcium absorption, it has been shown to decrease PTH levels (11). A previous study reported that vitamin D deficiency was 71.1% among children and adolescents [12].

In a study conducted with individuals living near the equator, it was reported that the serum vitamin D level was above 30 ng/ml in those who were exposed to sunlight without using sunscreen [13].

In studies conducted in Australia, Turkey, India, Lebanon, United Arab Emirates, and Saudi Arabia, the frequency of vitamin D deficiency in children and adults was reported to be approximately 30-50% [14,15].

In the study conducted by Erdal et al., in which 327 individuals aged 16-69 were included, it was accepted as <20 ng/ml for the diagnosis of vitamin D deficiency. In this study, the prevalence of vitamin D deficiency in women was found to be 75% [16]. Atli et al. found vitamin D deficiency (<30 ng/ml) in 54% of women and 18% of men staying in nursing homes in 2005. 4 [17].

In our study, the vitamin D levels of the patients at the time of diagnosis were significantly higher in men than in women. This situation can be explained by the fact that men are exposed to more sunlight than women in our study in the Sivas region, which cannot get enough sunlight in terms of its geographical location and climatic characteristics. There was no gender difference in the post-treatment vitamin D levels of our cases. In addition, men's ALP and creatinine values were higher than women's, and women's PTH values were higher than men's.

In a study using 12 ng/ml as the threshold value for vitamin D deficiency, 82% of elderly Greek women had vitamin D deficiency, compared with 18% of Norwegian elderly women. Although it receives less sun, it is thought that vitamin D-fortified foods and drugs, and even excess fish consumption in northern European countries, cause this condition [18].

In our study, vitamin D level was higher in patients aged 50-69 years compared to younger patients. In addition, ALP and PTH levels were higher in the elderly patient group. Post-treatment vitamin D levels did not differ significantly between patients separated by age groups.

One of the important indicators of vitamin D deficiency is an increase in serum PTH level. In vitamin D deficiency, parathormone increases due to the decrease in ionized calcium. It has been stated that there are changes in PTH values even if the vitamin D level is below 37 ng/ml [19]. In a study conducted by the "Longitudinal Aging Study Amsterdam" initiative on 1320 elderly men and women, it was shown that PTH increased to compensate for insufficient levels of vitamin D [20]. In studies conducted in France and the USA, a decrease in PTH was found with an increase in vitamin D after vitamin D treatment replacement in patients with vitamin D deficiency [13]. In our study, although a relationship was found between 25-OHD and ALP, Ca, P, and PTH, this relationship was not statistically significant. In the examinations performed after the treatment, the Ca values were found to be normal in all of the patients, and the PTH level was within the normal range in 91.2% of the patients.

The season and the angle of the sun also significantly affect the level of vitamin D produced in the skin. It has been reported that 6 IU of vitamin D is produced in this area when a square centimeter (cm2) skin surface is exposed to sunlight for one hour [21]. Accordingly, it has been reported that a newborn can produce 400 IU of vitamin D per hour even when only his face is exposed to sunlight [22]. In a study conducted in the Bolu region of Turkey, the 25-OH D level was studied only in the winter period and a significant decrease was found. In our study, the distribution of individuals according to the seasons in which vitamin D deficiency was detected was made. Accordingly, it was seen that the diagnosis of osteomalacia was made most frequently (60.4%) in the spring and at least in the autumn (10.7%). There was no significant difference between the vitamin D levels at the time of diagnosis according to the seasons.

Although the average of vitamin D level was highest in autumn, no significant difference was found between seasons. In regions with abundant sunlight, vitamin D deficiency occurs as a result of avoidance of sunlight due to the cultural habits of some ethnic groups [20]. When 21 people presenting with symptoms of osteomalacia in Saudi Arabia, a sunny country, were examined, it was shown that there were underlying risk factors such as insufficient dietary Ca and vitamin D intake, consumption of carbonated beverages, and daily exposure to the sun for less than 15 minutes on average [23]. In a study in which 212 individuals were included, vitamin D levels were measured in winter and summer. It was determined as 25.0±9.4 ng/ml. The seasonal variation increase was 13% in women and 14% in men, and these increases were found to be statistically significant ($p=0.0009$ in women, $p=0.033$ in men). It has been suggested that this seasonal level difference may be due to the long and cold winters and the shortening of daylight hours [8, 24].

It has been reported that serum vitamin D is lower in individuals with a high body mass index since vitamin D is sequestered in adipose tissue [5]. In previous studies, obese individuals were found to be more prone to vitamin D deficiency than normal individuals [25]. Interestingly, it has been suggested that low levels of vitamin D are less common in thin young girls with anorexia nervosa, and this may be due to the sequestration of vitamin D [26].

In this study, no significant relationship was found between BMI and vitamin D, Ca, P, ALP and creatinine. The PTH value in obese patients participating in the study was found to be higher than healthy and overweight patients. The reason for the lack of a significant relationship between vitamin D level and BMI may be due to the fact that the low level of vitamin D in the patients included in the study was affected by other reasons rather than BMI. However, patients with higher BMI after treatment had lower vitamin D levels. Vitamin D replacement is recommended for people who cannot adequately contact the sun. According to the Endocrine Society, it is recommended to apply 50,000 IU/week of vitamin D for 8 weeks, followed by maintenance therapy of 1500-2000 IU/day for 8 weeks, in order to increase 25-OHD levels above 30 ng/ml in people with vitamin D deficiency [27].

According to the vitamin D levels measured at the time of diagnosis and during the follow-ups, 300,000 IU oral vitamin D3 treatment was given once a week to patients with severe deficiency, once every 2 weeks to patients with deficiency, and once a month to patients with insufficiency. In this study, although we applied treatment at a higher dose and duration than recommended, 14.3% of our patients still had serious deficiency. This demonstrates the importance of intensive treatment and follow-up in order to normalize vitamin D levels. It has been shown that malabsorption conditions such as celiac and biliary tract diseases, which impair oral vitamin D absorption, should also be kept in mind in those who do not increase despite treatment.

Limitations

Inclusion of people from different sociocultural levels in the study without standardizing clothing style, diet and sun exposure time in normal weight, women may explain the differences in vitamin D levels. In addition, the presence of undiagnosed celiac disease, inflammatory bowel disease and biliary tract disease, which are common in the community and may cause malabsorption, may also cause vitamin D deficiency.

It is thought that in some of the patient groups that we could not reach the target value as a result of the treatment, compliance with the treatment could not be achieved in some of them, and that in some of them there were conditions that complied with the treatment, but that should be investigated with further investigations, such as underlying malabsorption and biliary tract diseases. Although the number of patients included in the study was high, the results of the study cannot be generalized to the general population because it included patients who applied to our outpatient clinic.

Conclusions

The severe vitamin D deficiency was found in 75.4% of the current study population. The diagnosis of osteomalacia was found mostly in the spring period. After 4 weeks of treatment, only 40% of patients had normal levels of vitamin D. Study findings showed that geographical and cultural differences should be taken into account in addition to existing treatment guidelines to reduce vitamin D deficiency. In patients with severe vitamin D deficiency (10 ng/ml<), especially in the period of winter, when sunlight cannot be benefited sufficiently, 300,000 IU of vitamin D supplementation may be done weekly until the vitamin D level reaches the normal level.

Conflict of interest: None

Author Contributions		Author Initials
SCD	Study Conception and Design	SG, MFK, OG
AD	Acquisition of Data	SG, MFK, OG
AID	Analysis and Interpretation of Data	SG, MFK, OG
DM	Drafting of Manuscript	SG, MFK, OG
CR	Critical Revision	SG, MFK, OG

Financial support: None
Acknowledgments: None
Prior publication: It has not been published in any journal before. It has not been presented in any scientific congress or meeting.

References

1. Saponaro F, Saba A, Zucchi R. An update on vitamin d metabolism. Int J Mol Sci 2020;21(18):6573.https://doi.org/10.3390/ijms21186573
2. Chun RF, Shieh A, Gottlieb C, Yacoubian V, Wang J, Hewison M, et al. Vitamin D binding protein and the biological activity of vitamin D. Front Endocrinol (Lausanne) 2019;10:718. https://doi.org/10.3389/fendo.2019.00718
3. Silva MC, Furlanetto TW. Intestinal absorption of vitamin D: a systematic review. Nutr Rev 2018;76(1):60-76. https://doi.org/10.1093/nutrit/nux034
4. Uday S, Högler W. Nutritional rickets & osteomalacia: A practical approach to management. Indian J Med Res 2020;152(4):356-67. https://doi.org/10.4103/ijmr.ijmr_1961_19
5. Onalan E, Yakar B. The effect of vitamin D level on body composition and metabolic parameters in adults with different body mass index. Med Sci 2020;9(2):370-5. http://doi.org/10.5455/medscience.2019.08.9198
6. Awal W, Bindra R, Price N, Sadler A, Robinson A, Hymer I, Chen J. Vitamin D deficiency in proximal femur fracture patients of South-East Queensland. Australas J Ageing. 2020;39(3):271-7. https://doi.org/10.1111/ajag.12791
7. Goktaş O, Ersoy C, Ercan I, Can FE. Vitamin D status in the adult population of Bursa-Turkey. Eur J Gen Pract. 2020;26(1):156-2. https://doi.org/10.1080/13814788.2020.1846712
8. Solak I, Cihan FG, Mercan S, Kethuda T, Eryilmaz MA. Evaluation of 25-Hydroxyvitamin D Levels in Central Anatolia, Turkey. Biomed Res Int 2018;2018:4076548. https://doi.org/10.1155/2018/4076548
9. Alpdemir M, Alpdemir MF. Vitamin D deficiency status in Turkey: A meta-analysis. Int J Med Biochem 2019;2(3):118-31. https://dx.doi.org/10.14744/ijmb.2019.04127
10. Yakar B, Kaya MO. Vitamin D deficiency during pregnancy in Turkey and the effect of the sunlight: a systematic review and meta-analysis. Turk J Biochemistry 2021;46(2):129-35. https://doi.org/10.1515/tjb-2020-0059
11. Vieth R. Vitamin D supplementation: cholecalciferol, calcifediol, and calcitriol. Eur J Clin Nutr 2020;74(11):1493-7. https://doi.org/10.1038/s41430-020-0697-1
12. Rastad H, Mahdavi Gorabi A, Qorbani M, Seif E, Asayesh H, Motlagh ME, Heshmat R, Kelishadi R. Prevalence and determinants of vitamin D deficiency in Iranian children and adolescents: the CASPIAN-V study. J Diabetes Metab Disord 2021;20(1):383-9. https://doi.org/10.1007/s40200-021-00757-8
13. Neale RE, Khan SR, Lucas RM, Waterhouse M, Whiteman DC, Olsen CM. The effect of sunscreen on vitamin D: a review. Br J Dermatol 2019;181(5):907-15. https://doi.org/10.1111/bjd.17980
14. Walter Siegenthaler. Differential diagnosis in internal medicine from symptom to diagnosis. Germany; Thieme, 2007:371-6
15. Mark LS, Simon S, Valerie ES. Vitamin D. Aust Fam Physician. 2008;37:1002-5.
16. Yeşiltepe-Mutlu G, Aksu ED, Bereket A, Hatun S. Vitamin D Status Across Age Groups in Turkey: Results of 108,742 samples from a single laboratory. J Clin Res Pediatr Endocrinol 2020;12(3):248-55. https://doi.org/10.4274%2Fjcrpe.galenos.2019.2019.0097
17. Sezgin G, Ozturk G, Turkal R, Caykara B. Vitamin D levels of outpatients admitted to a university hospital in the Marmara region of Turkey Over 3 Years. J Med Biochem. 2019;38(2):181-7. https://doi.org/10.2478%2Fjomb-2018-0027
18. Roth DE, Abrams SA, Aloia J, Bergeron G, Bourassa MW, Brown KH, et al. Global prevalence and disease burden of vitamin D deficiency: a roadmap for action in low- and middle-income countries. Ann N Y Acad Sci. 2018;1430(1):44-79. https://doi.org/10.1111/nyas.13968
19. Thomas MK, Lloyd-Jones DM, Thadhani RI, Shaw AC, Deraska DJ, Kitch BT, et al. Hypovitaminosis D in medical in patients. N Engl J Med. 1998;338:777-83. https://doi.org/10.1056/nejm199803193381201
20. Heath DA, Shaw NJ. Calcium and bone metabolism. In:Brook CGD, Hindmarsch PC, editors. Clinical Pediatreic Endocrinology Oxford: Blackwell science Press; 2001;377-89.
21. Kechichian E, Ezzedine K. Vitamin D and the skin: an update for dermatologists. Am J Clin Dermatol. 2018;19(2):223-35. https://doi.org/10.1007/s40257-017-0323-8

22. Pludowski P, Holick MF, Grant WB, Konstantynowicz J, Mascarenhas MR, Haq A, et al. Vitamin D supplementation guidelines. J Steroid Biochem Mol Biol 2018;175:125-35. https://doi.org/10.1016/j.jsbmb.2017.01.021
23. Bouillon R, Antonio L. Nutritional rickets: Historic overview and plan for worldwide eradication. J Steroid Biochem Mol Biol 2020;198:105563. https://doi.org/10.1016/j.jsbmb.2019.105563
24. Eloi M, Horvath DV, Szejnfeld VL, Ortega JC, Rocha DA, Szejnfeld J, Castro CH. Vitamin D deficiency and seasonal variation over the years in São Paulo, Brazil. Osteoporos Int 2016;27(12):3449-56. https://doi.org/10.1007/s00198-016-3670-z
25. Fiamenghi VI, Mello ED. Vitamin D deficiency in children and adolescents with obesity: a meta-analysis. J Pediatr (Rio J) 2021;97(3):273-9. https://doi.org/10.1016/j.jped.2020.08.006
26. Gatti D, El Ghoch M, Viapiana O, Ruocco A, Chignola E, Rossini M, et al. Strong relationship between vitamin D status and bone mineral density in anorexia nervosa. Bone 2015;78:212-5. https://doi.org/10.1016/j.bone.2015.05.014
27. Holick MF. The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention. Rev Endocr Metab Disord 2017;18(2):153-65. https://doi.org/10.1007/s11154-017-9424-1