



# Effect of vitamin D levels on radiographic knee osteoarthritis and functional status

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## ABSTRACT

**Objectives:** This study aims to investigate the effect of serum levels of 25 hydroxyvitamin D (25(OH)D) in patients with primary knee osteoarthritis (OA) and to assess its relationship with the radiographic grading and functional status.

**Patients and methods:** Serum 25(OH)D levels were measured in 107 patients (90 females, 17 males; mean age 63.0±9.6 years; range, 40 to 86 years) with primary knee OA. Radiographic grading was based on the Kellgren-Lawrence Grading Scale and the Osteoarthritis Research Society International (OARSI) Atlas Grading Scale, while the functional status was assessed using the Lequesne indices and Turkish version of the Knee Injury and Osteoarthritis Outcome Score-Physical Function Short-Form (KOOS-PS). Pain was evaluated using the Visual Analog Scale for Pain (VAS-Pain). Data including age, sex, disease duration, body mass index (BMI), and pain severity were recorded.

**Results:** The mean 25(OH)D level was 13.4±10.6 ng/mL, and 90 patients (84.1%) had vitamin D deficiency. The presence of severe osteophytes was observed in 67 patients (62.6%) and 85 patients (79.4%) had Grade 2-3 joint space narrowing (JSN). The mean KOOS-PS and Lequesne scores were 40.1±12.3 and 12.9±3.6, respectively. There was no correlation between serum 25(OH)D levels and functional status.

**Conclusion:** Our study results show that serum 25(OH)D level is not related to the severity of the radiographic knee OA grading or to the functional assessment. Age and BMI are the factors affecting the radiological knee OA severity, while age, sex, BMI, and pain severity are the main determinants of the functional status.

**Keywords:** Functional status; knee osteoarthritis; radiographic grading; vitamin D.

Osteoarthritis (OA) is a disease of all elements of the synovial joints, while the mainly affected components are cartilage and subchondral bones. It is known as the most common cause of functional failure in elderly. Although the pathogenesis of the disease is not clear, there are molecular evidences about the coordinated release of cytokines and inflammatory mediators from elements of synovial joints. Various risk factors such as mechanical stress, biochemical abnormalities, genetic predisposition, and metabolic disorders have been suggested for the progression of OA.<sup>[1,2]</sup>

Vitamin D is a steroid hormone which plays a central role in calcium and phosphorus metabolism and bone mineralization.<sup>[3]</sup> Normal bone metabolism is related with the presence of vitamin D.<sup>[4]</sup> In recent years, insufficient levels of vitamin D has been shown

to be associated with many chronic diseases, including common cancers, cardiovascular diseases, metabolic syndrome, autoimmune diseases, changes in cartilage composition, subchondral lesions, and progression of knee OA.<sup>[3,5]</sup>

There are many studies about the association between serum 25 hydroxyvitamin D (25(OH)D) deficiency and knee OA. Previously, a significant association between 25(OH)D with knee OA has been reported.<sup>[5]</sup> It has been also suggested that serum 25(OH)D should be measured in any patients with symptoms suggestive of knee OA, particularly at the initial stage of disease.<sup>[5]</sup> However, the level of 25(OH)D seems not to be related to the severity of the radiographic knee OA grading, cartilage loss, or functional assessment in knee OA.<sup>[6,7]</sup>

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In the present study, we aimed to investigate the effect of serum levels of 25(OH)D in patients with primary knee OA and to assess its association with the radiographic grading and functional status of the patients.

## PATIENTS AND METHODS

This cross-sectional study included a total of 107 patients (90 females, 17 males; mean age  $63.0 \pm 9.6$  years; range, 40 to 86 years) who were admitted to our Physical Medicine and Rehabilitation outpatient clinic and were diagnosed with primary knee OA between March 2015 and September 2015. The diagnosis of primary knee OA was based on the American College of Rheumatology (ACR) criteria.<sup>[8]</sup> Patients with inflammatory arthritis, intra-articular neoplasms, osteonecrosis, trauma, paresis, neuropathy, mental disorders, history of previous knee surgery, and history of intra-articular intervention or physical therapy within the past six months were excluded from the study. All patients included were informed about the study, and their written informed consent was obtained. The study protocol was approved by the institutional Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Demographic characteristics including age, sex, and disease duration were recorded. In both knees, the range of motion (ROM) was measured by goniometry and anteroposterior and lateral knee radiographs were taken during weight-bearing. Radiographic grading of OA was performed according to the Kellgren-Lawrence (K-L) criteria<sup>[9]</sup> by an experienced radiology specialist. All patients were scored for joint space narrowing (JSN) and osteophytes separately on a scale from 0 to 3 (0=normal; 3=severe) according to the Osteoarthritis Research Society International (OARSI) Atlas.<sup>[10]</sup> Pain was evaluated using the Visual Analog Scale for Pain (VAS-Pain), 0-10 cm and the severity of pain was assessed.<sup>[11]</sup> All patients were also assessed for function using the Lequesne indices<sup>[12]</sup> and Turkish version of the Knee Injury and Osteoarthritis Outcome Score-Physical Function Short-Form (KOOS-PS).<sup>[13]</sup>

Intact parathyroid hormone (PTH) (reference: 12-88 pg/mL), bone-specific alkaline phosphatase (ALP) (9-116 IU/L), and 25(OH)D<sub>3</sub> (30-100 ng/mL) levels in the patient and the control groups were analyzed using standard methods. In addition, C-reactive protein (CRP) with the nephelometric method (0.2-5.0 mg/L), erythrocyte sedimentation

rate (ESR) with the Westergren method (0-20 mm/h), serum total calcium, ionized calcium, urea, creatinine, phosphorous, total protein, and albumin levels were measured with the standard autoanalyzer. The vitamin D level was defined as deficient when 25(OH)D was  $<20$  ng/mL.<sup>[14,15]</sup> The patients were divided into two groups according to 25(OH)D deficiency. Clinical, laboratory, and radiographic characteristics were analyzed between the two groups.

### Statistical analysis

Statistical analysis was performed using the PASW version 18.0 software (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was used to for the normality test. According to the results, age, body mass index (BMI), and Lequesne variables were normally distributed. Non-parametric tests were used due to the unequal variances. Descriptive statistics were expressed in mean  $\pm$  standard deviation (SD), and median (min-max) for continuous variables. The Student's t-test was used to analyze significant differences for normal distribution between low ( $<20$  ng/mL) and normal vitamin D groups, while the Mann-Whitney U test was used for the abnormally distributed variables. The chi-square and Fisher's exact tests were done to evaluate associations among categorical variables. Each of the JSN and osteophytes scores were divided into two groups: the first group consisted of Grade 1 and 2 scores, while the second group consisted of Grade 3 scores according to the OARSI Atlas Grading Scale. Variable selection was performed with univariate analysis and at least moderately significant variables (i.e., age, disease duration, BMI, and vitamin D) were selected for the multivariate logistic regression analysis. The Spearman correlation test was used to analyze relationships between the functional scores and continuous variables. Multiple linear regressions were also used to examine the association with risk factors and functional scores. The KOOS-PS and Lequesne scores were analyzed in male and female groups using the Mann-Whitney U test. A *p* value of  $<0.05$  was considered statistically significant.

## RESULTS

The demographic and clinical characteristics of all patients are shown in Table 1. Serum calcium, PTH, and albumin levels were within normal limits in all patients. The mean value of 25(OH)D level was  $13.4 \pm 10.6$  ng/mL, and 90 patients (84.1%) were vitamin D deficient. Radiographic findings based on the OARSI Atlas Grading Scale revealed JSN in all

**Table 1.** Demographic and clinical characteristics of patients with knee osteoarthritis

	n	%	Mean±SD	Median	Min-Max
Age (year)			63.0±9.6		
Sex					
Female	90	84.1			
Male	17	15.9			
Body mass index (kg/m <sup>2</sup> )			31.4±6.1		
Duration of disease (month)				60	1-240
Calcium (mmol/L)				9.60	7.70-78.00
Vitamin D (ng/mL)				11.90	2.50-67.90
Lequesne Index			12.9±3.6		
KOOS-PS				40.30	14.80-62.00
Visual Analog Scale-pain				7.00	4.00-10.00
Kellgren-Lawrence Grade					
1	4	3.7			
2	33	30.8			
3	48	44.9			
4	22	20.6			
OARSI-JSN					
1	22	20.6			
2	52	48.6			
3	33	30.8			
OARSI-osteophytes					
1	40	37.4			
2	46	43.0			
3	21	19.6			

SD: Standard deviation; Min: Minimum; Max: Maximum; KOOS-PS: Knee Injury and Osteoarthritis Outcome Score-Physical Function Short-Form; OARSI: Osteoarthritis Research Society International Atlas.

**Table 2.** A comparison of the patients with and without vitamin D deficiency

	Group 1 (n=90) (25(OH)D <20 ng/mL)					Group 2 (n=17) (25(OH)D ≥20 ng/mL)					p
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	
Age (year)			62.6±9.9					65.0±7.5			0.25
Sex											0.46
Female	75					15					
Male	15					2					
Body mass index (kg/m <sup>2</sup> )			31.7±6.0					29.8±6.3			0.37
Duration of disease (month)				48.00	3.00-240.00				60.00	1.00-240.00	0.80
Lequesne Index			12.9±3.5					13.1±3.8			0.65
KOOS-PS				39.45	14.80-62.00				40.30	14.80-62.00	0.59
Visual Analog Scale-pain				7.00	4.00-10.00				7.00	4.00-9.00	0.47
Kellgren-Lawrence Grade											0.83
1	3	3.3				1	5.9				
2	27	30.0				6	35.3				
3	42	46.7				6	35.3				
4	18	20.0				4	23.5				
OARSI-JSN											0.80
1	18	20.0				4	20.6				
2	45	50				7	41.2				
3	27	30				6	35.3				
OARSI-osteophytes											0.66
1	32	35.6				8	47.1				
2	40	44.4				6	35.3				
3	18	20.0				3	17.6				

SD: Standard deviation; Min: Minimum; Max: Maximum; KOOS-PS: Knee Injury and Osteoarthritis Outcome Score-Physical Function Short-Form; JSN: joint space narrowing; OARSI: Osteoarthritis Research Society International Atlas.

**Table 3.** Multivariate logistic regression analysis showing the association between radiographic osteoarthritis and risk factors

	B	SE	p*	Exp(B)	95% CI	
JSN						
2 (Grade 3)**						
Intercept	-14.082	3.297	0.000			
Age	0.131	0.034	0.000	1.140	1.066	1.218
Body mass index	0.140	0.046	0.003	1.150	1.050	1.206
Vitamin D	-0.004	0.023	0.879	0.996	0.952	1.043
Disease duration	0.006	0.004	0.168	1.006	0.998	1.014
Osteophytes						
2 (Grade 3)**						
Intercept	-8.537	2.851	0.003			
Age	0.077	0.030	0.010	1.081	1.019	1.146
Body mass index	0.072	0.045	0.107	1.075	0.985	1.174
Vitamin D	-0.029	0.032	0.360	0.971	0.912	1.034
Disease duration	0.002	0.004	0.595	1.002	0.994	1.011

B: Regression coefficient; SE: Standard error; Exp(B): Odds ratio; CI: Confidence interval; JSN: Joint space narrowing; \* p<0.05; \*\* The reference category 1.00 (Grade 1 and 2 according to the Osteoarthritis Research Society International Atlas).

patients, while JSN of Grade 2-3 was seen in 85 patients (79.4%) and 67 patients (62.6%) had severe osteophytes in the medial and lateral tibiofemoral compartments of both right and left knees. There was no significant difference in the age, BMI, duration of knee OA, function and radiographic grading between vitamin D deficient and normal groups (Table 2).

Risk factors for radiographic knee OA (OARSI-JSN and osteophytes) such as age, disease duration, BMI, and 25(OH)D deficiency were analyzed using multivariate logistic regression analysis. A significant relationship was found between the JSN with age and BMI, while only age was found to be associated with osteophytes (Table 3). However, 25(OH)D levels were not associated with JSN or osteophytes in the multivariate logistic regression analyses.

Furthermore, the KOOS-PS and Lequesne scores used to assess the functional status were not found to be significantly different between the groups. The factors associated with the functional scores were analyzed using the correlation analysis and pain, BMI, disease duration, and age were found to be associated with both indices (p<0.05). However, there was no correlation between the vitamin D levels and functional scores. In the multiple linear regression analyses, on the other hand, there was an association between the functional scores and age, BMI, and pain (Table 4).

The KOOS-PS and Lequesne scores were analyzed in categories according to sex. Although the Lequesne scores were found to be worse in females, there was no significant difference. In addition, the mean Lequesne scores were 10.5±3.3 (range 4 to 15) in males and

**Table 4.** Functional status of patients with risk factors based on the multiple linear regression analysis

	B	SE	Standard B (β)	p	95% CI	
KOOS-PS						
Constant	-25.206	9.494		0.009	-44.04	-6.372
Age	0.297	0.100	0.231	0.004*	0.098	0.495
Body mass index	0.544	0.162	0.270	0.001*	0.222	0.866
Vitamin D	0.090	0.089	0.078	0.315	-0.087	0.268
Disease duration	0.008	0.016	0.038	0.628	-0.024	0.040
Visual Analog Scale-pain	3.964	0.602	0.511	0.000*	2.769	5.159
Lequesne						
Constant	-7.265	2.821		0.011	-12.860	-1.669
Age	0.124	0.030	0.333	0.000*	0.065	0.183
Body mass index	0.166	0.048	0.285	0.001*	0.071	0.262
Vitamin D	0.028	0.027	0.084	0.295	-0.025	0.081
Disease duration	0.004	0.005	0.075	0.353	-0.005	0.014
Visual Analog Scale-pain	0.922	0.179	0.409	0.000*	0.567	1.277

B: Regression coefficient; SE: Standard error; CI: Confidence interval; KOOS-PS: Knee Injury and Osteoarthritis Outcome Score-Physical Function Short-Form; \* p<0.05.

13.4±3.4 (range 5 to 21) in females (p=0.003). The median KOOSPS scores was 40.30 (range 14.80 to 62.00) in males and 37.000 (range 14.80 to 54.40) in females (p=0.079).

## DISCUSSION

Osteoarthritis is the most common form of arthritis, characterized by cartilage loss, thereby, leading to the functional failure.<sup>[16]</sup> Vitamin D is a hormone which affects bone metabolism and non-bony tissues. The relationship between vitamin D and knee OA has been studied previously. In the literature, although there are studies supporting the effect of vitamin D deficiency on knee OA progression, no association has been reported in several studies.<sup>[5-7,16,17]</sup> In this study, therefore, we investigated the effect of serum levels of 25(OH)D in patients with primary knee OA and assessed its association with the radiographic grading and functional status of the patients.

Vitamin D deficiency, which is defined as serum 25(OH)D levels of <20 ng/mL, has been reported with a rate ranging from 2.3 to 60%.<sup>[18-22]</sup> Its prevalence varies according to the age and sex of the patient, ethnicity and geographical factors, and in those living in nursing homes. In the Turkish population, vitamin D deficiency ranges between 37.9 and 71.7%.<sup>[23-26]</sup> In this study, the mean 25(OH)D level was 13.4±10.6, and 90 patients (84.1%) were vitamin D deficient, indicating a higher prevalence compared to previous studies conducted in Turkey. This result may be due to the high mean age of the patients, high rates of housewives included and of those living in the rural areas. In addition, the sun exposure may be inadequate, as the majority of the women wear long garments and headscarves.

Some hypotheses have been advocated about the influence of vitamin D level on the development or progression of OA. Although the underlying mechanism still remains unclear, it is considered that vitamin D deficiency can affect the chondrocytes, the condition of articular cartilage, increasing the PTH and bone turnover.<sup>[17]</sup> Furthermore, vitamin D stimulates the synthesis of proteoglycan by the mature articular cartilage and, thus, may affect the articular cartilage metabolism.<sup>[27]</sup> However, several studies about vitamin D and OA relationship reveal controversial results. Heidari et al.<sup>[5]</sup> reported that 25(OH)D was associated with symptomatic knee OA in patients aged <60 years. In a review including 15 studies, a moderate evidence was found indicating that low levels of 25(OH)D were associated with an increased progression

of radiographic OA.<sup>[16]</sup> In another study including 880 randomly-selected patients, low vitamin D levels were associated with JSN.<sup>[28]</sup> Bergink et al.<sup>[17]</sup> also evaluated 25(OH)D levels, dietary vitamin D intake, and radiographic OA in 1,248 patients and they reported higher JSN scores in the patients with vitamin D deficiency.

Although it is thought that vitamin D has an effect on chondrocytes and articular cartilage, several studies have shown no association between vitamin D status and the risk of cartilage loss and severity of radiographic knee OA grading.<sup>[6,7]</sup> Muraki et al.<sup>[27]</sup> reported that lower 25(OH)D levels might be associated with increased knee pain rather than radiographic changes. In another study including 1,644 female twins, the authors found no association between the JSN and vitamin D levels in the patients who had an evidence of increased bone turnover, increased PTH levels, and decreased vitamin D levels.<sup>[29]</sup> In our study, radiographic X-ray grading was evaluated with two different methods (i.e., Kellgren-Lawrence and OARSI). Although the majority of the patients with knee OA had vitamin D deficiency, we found no relationship between vitamin D levels and radiographic severity. However, age and BMI were found to affect the radiographic scores in our study.

Furthermore, functional disability is one of major public health problems in elderly population. Knee OA provides major contribution to the joint function and disability in the general population.<sup>[30]</sup> Factors associated with disability in knee OA include age, low educational status, obesity, female sex, comorbidity, radiographic severity, and pain.<sup>[31]</sup> The risk of disability also increases with the presence of knee pain.<sup>[30-32]</sup> There are also several studies reporting a relationship between pain and physical functions in patients with knee OA.<sup>[30-32]</sup> In previous studies, knee pain, age, and obesity were found more evident determinants of functional disability than the severity of radiographic knee OA.<sup>[30-32]</sup> Consistent with the literature, we also found a positive correlation between the functional disability and pain severity, BMI, and age.

In recent years, the relationship between vitamin D deficiency and functional disability has been studied.<sup>[6,33-35]</sup> Sanghi et al.<sup>[34]</sup> suggested a slight, but statistically significant clinical benefit related to pain and function with vitamin D treatment in patients with knee OA. Glover et al.<sup>[35]</sup> also demonstrated that the participants with adequate vitamin D had significantly less knee OA pain and better functional

performance than those with vitamin D deficiency. However, Al-Jarallah et al.<sup>[6]</sup> found no association between vitamin D and functional assessment in the patients with primary knee OA. Although functional status was evaluated with two different indices in the present study, we found no association between the functional scores and vitamin D levels. The higher mean age (>60 years) and radiographic OA Grade in both of vitamin D insufficient and normal groups may have affected the functional disability, rather than vitamin D levels.

The small sample size and lack of a longitudinal assessment are the main limitations to this study.

In conclusion, our study results suggest that there is no association between vitamin D levels and severity of knee OA and functional status. Age and BMI are the main risk factors which affect the radiographic knee OA severity, while age, sex, BMI, and pain are the main determinants for the functional status.

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