

The Effects Of vitamin D On Muscle Strength And Functional Status Of The Elderly Patients With Knee Osteoarthritis

Gonartrozlu Yaşlı Hastada D Vitamininin Kas Gücü ve Fonksiyonel Durum Üzerine Etkisi

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ÖZET

AMAÇ: Bu çalışmanın amacı, diz osteoartriti olan yaşlı hastaların serum D vitamini düzeylerinin ağrı şiddeti, kas gücü ve fonksiyonel durumu üzerindeki etkilerini değerlendirmektir.

GEREÇ VE YÖNTEM: Çalışmaya diz osteoartriti seksen bir hasta dahil edildi. Ağrı görsel analog skala (VAS) ile ölçüldü. Ağrı, eklem sertliği ve fiziksel fonksiyonu değerlendirmek için Western Ontario ve McMaster Üniversitesi Artrit İndeksi (WOMAC) kullanıldı. Maksimum izokinetik kas kuvveti ve pik tork/vücut ağırlığı değerleri ölçüldü.

BULGULAR: Hastalar 25 (OH) D vitamini seviyelerine göre iki gruba ayrıldı: Grup 1; 25 (OH) D vitamini seviyeleri 20ng/ml'nin altında ve Grup 2; 20ng/ml'nin üstünde olanlardan oluşuyordu. VAS skorları, ortalama WOMAC ağrısı, fonksiyon ve toplam skorlar Grup 1'de Grup 2'ye göre daha yüksekti. Dizdeki ekstansör ve fleksör kasların maksimum izokinetik kas kuvveti ve pik tork/vücut ağırlığı değerleri Grup 1'de Grup 2'ye göre anlamlı olarak daha düşüktü (tüm değerler için $p < 0.001$).

SONUÇ: D vitamini eksikliği, diz osteoartriti olan hastalarda ağrı, kas güçsüzlüğü ve fonksiyon kaybına katkıda bulunan bir faktör gibi görünmektedir.

Anahtar Kelimeler: yaşlı, fonksiyon, izokinetik, diz, kas, osteoartrit, ağrı, güç, D vitamini

ABSTRACT

OBJECTIVE: This study aimed to evaluate the effects of vitamin D levels on pain intensity, muscle strength, and functional status of elderly patients with osteoarthritis of the knee.

MATERIALS AND METHODS: Eighty-one patients with osteoarthritis of the knee were enrolled in this study. The pain was measured with a visual analog scale (VAS). Western Ontario and McMaster University Arthritis Index (WOMAC) was used to evaluate pain, stiffness, and physical function. The maximum isokinetic muscle strength and the peak torque/body weight values were measured.

RESULTS: The patients were divided into two groups according to their 25 (OH) vitamin D levels: Group 1 consisted of patients whose 25 (OH) vitamin D levels were below 20 ng/ml. Group 2 comprised those with levels above 20 ng/ml. The VAS scores, the mean WOMAC pain, function, and total scores were higher in Group 1 than Group 2. The maximal isokinetic muscle strength of the extensor and flexor muscles of the knee and the peak torque/body weight values were significantly lower in Group 1 than in Group 2 ($p < 0.001$ for all values).

CONCLUSION: Vitamin D deficiency seems to be a factor contributing to pain, muscle weakness, and disability in patients with knee osteoarthritis.

Keywords: elderly, function, isokinetic, knee, muscle, osteoarthritis, pain, strength, vitamin D

INTRODUCTION

Osteoarthritis (OA) is an adult joint disease with common presentations of pain and loss of function. It is most often seen in people older than 65, and the knee is the most frequently affected site. OA is a non-inflammatory disease that results in metabolic, structural, and biochemical

changes in the joints' cartilage, affecting the subchondral bone, ligaments, capsule, synovial membrane and the surrounding muscles. It leads to pain, disability, decreased muscle strength and limited range of motion (1, 2).

Vitamin D deficiency is common in people over 65 years. It leads to osteomalacia that causes bone pain. Skeletal

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muscles have vitamin D receptors and its deficiency can induce muscle weakness. In different clinical trials, vitamin D deficiency was found to be related to non-specific muscle, bone and joint pain, muscle weakness, fatigue, chronic somatic complaints, depression and anxiety (3, 4).

In knee OA, weakness in the quadriceps and hamstring muscle groups leads to pain and a decrease in functional capacity. In late stages, muscle atrophy and instability occur and the pain worsens. In several studies performed on elderly OA patients, a decrease in functional capacity, muscle strength, endurance, and angular velocity have been reported (5-7). The effects of vitamin D on muscle strength have been studied in healthy older people, hemodialysis patients and athletes (8-11). In a systematic review published in 2017, the effect of the use of vitamin D on the treatment of knee osteoarthritis was mainly focused on the pain parameter and it was reported that it did not affect pain (12). In this study, we aimed to evaluate the effects of vitamin D levels on pain, muscle strength and functional status of knee OA patients over 65 years.

MATERIAL & METHODS

Study Design:

The current study employed a cross-sectional descriptive design to compare knee osteoarthritis patients by their vitamin D levels.

Participants:

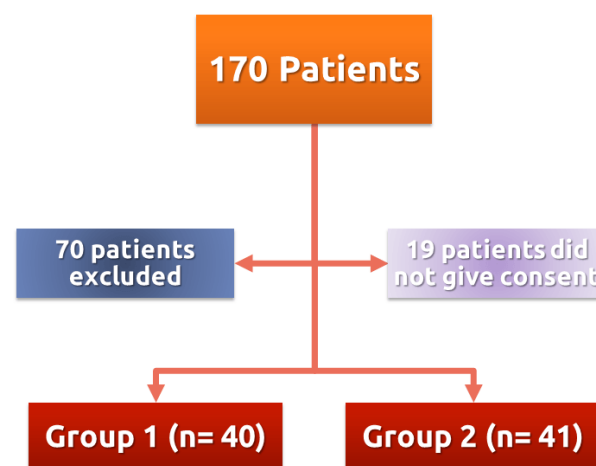
One hundred-seventy knee OA patients over 65 years of age, who had been admitted to the outpatient clinic from January 2014 to May 2015, fulfilled the American College of Rheumatology (ACR) knee OA criteria (13), and had grade 1-3 knee OA according to the Kellgren Lawrance radiological classification were screened (14).

The inclusion and exclusion criteria for participants:

The patients who had a somatic, psychiatric or mental illness limiting their cooperation, those with contraindications to isokinetic testing (high-grade osteoporosis, joint instability, fractures, joint or bone malignancy, severe peripheral vascular disease, pregnancy, symptomatic or uncontrolled hypertension, high-grade limitations in the joint's range of motion), those who had an inflammatory rheumatic disease, severe pain during isokinetic testing, previous knee surgery, vitamin D supplementation within the last year, a gastrointestinal disease affecting absorption (e.g., Crohn's Disease,

Whipple's Disease, Cystic Fibrosis, and Celiac's Disease), chronic liver disease, renal insufficiency and nephrotic syndrome, and those patients that were using medication affecting vitamin D levels (e.g., antiepileptics, glucocorticoids, and rifampin) were excluded from the study. Other exclusion criteria included having a neuromuscular disease that could affect the balance and muscle strength, prominent anemia, abnormal parathyroid hormone (PTH) levels and hypo/hyperthyroidism. Seventy patients who did not meet the inclusion criteria and 19 patients who did not consent for the isokinetic testing were excluded from the study. As a result, 81 elderly patients with bilateral knee OA were recruited (total 162 knee joints) (Figure 1).

Figure 1. Patients distribution



Instruments:

The demographical properties of the patients [age, gender, weight, height, body mass index (BMI), and duration of illness] were recorded. The knee OA was graded according to the Kellgren-Lawrence Scale with anteroposterior and lateral knee radiograms taken in the erect position and during extension. The severity of pain in the last ten days during rest and motion was evaluated using the 0-10 Visual Analogue Scale (VAS) (0=no pain; 10=most severe pain). The Turkish version of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scale was used to evaluate pain, stiffness, and reduced physical function. In this scale, high WOMAC scores indicate increased pain and stiffness, and poor physical function (15).

The levels of serum calcium, phosphorus, alkaline phosphatase, albumin, corrected calcium, parathyroid hormone, and 25 (OH) vitamin D were measured using Mass Spectrometry (Zivak device). The reference values of

25 (OH) vitamin D levels of our laboratory were as follows; severe deficiency if <10 ng/ml, mild deficiency if 10-24 ng/ml, optimum if 25-80 ng/ml, and toxic if >150 ng/ml for. The patients were divided into two groups according to their serum 25 (OH) vitamin D levels: Those who had levels lower than 20 ng/ml constituted Group 1 while patients with levels higher than 20 ng/ml formed Group 2.

Isokinetic contraction is the contraction type at the full range of motion during movement, with constant angular velocity and maximum tension. It is evaluated using isokinetic test devices. This test allows the quantitative measurement of the performance of the musculoskeletal system (16).

Before the evaluation of isokinetic muscle strength, to warm up, the patients walked on a treadmill for five minutes. The range of motion of the knees of the patients was determined through maximum extension and flexion. For the test protocol, the concentric/concentric motion was used. Three repetitive tests were undertaken before the test recording. The test was performed at the angular velocities of 60°/s and 180°/s. The patients were allowed a 15-second rest between the two sets. The maximum isokinetic muscle strength (peak torque, Nm), and peak torque/body weight (Nm/kg) of extensor and flexor muscles in both extremities were measured in a concentric-concentric combined test using an isokinetic dynamometer (Biodex System pro4. New York, USA). For the isokinetic measurements, the default settings of the device consisting of a 60°/sec strength test and 180°/sec power test were used. Five repetitions in the 60°/sec protocol, 10 repetitions in the 180°/sec protocol, and the peak torque and peak torque/body weight values were recorded.

The study was approved by the local ethical committee. All the patients provided written informed consent.

Statistical Analysis:

The analysis of the data was performed with SPSS 19.0 for Windows (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.). The Shapiro-Wilk test was utilized to determine whether the distribution of the numerical variables was within the normal range. Definitive statistics were average ± standard deviation or median (minimum-maximum) for numerical variables and the number and percentages of cases for categorical variables.

The significance of the difference in the averages of the groups was evaluated using the Student's t-test. For median values, the same difference was evaluated with the Mann Whitney U test. The categorical variables were analyzed by Pearson's chi-square or probability rate tests. Multiple stepwise linear regression analyses were conducted to identify factors affecting the peak torque values of the right-left knee extension and flexion. A level of p<0.05 was considered statistically significant.

RESULTS

Eighty-one patients with OA of the knee aged 65 to 71 years were enrolled in the study. The demographical and clinical characteristics of the two groups are shown in Table 1. There was no statistically significant difference between the groups according to age, gender, and BMI (p>0.05). The mean vitamin D levels were 10.98±4.68 (3.6-19.97) ng/ml in Group 1 and 42.99±17.13 (21.2-79.7) ng/ml in Group 2. The mean disease duration in Group 1 was significantly longer compared to Group 2 (p=0.025).

Table 1. Demographics of the patients

	Group 1 (n=40)	Group 2 (n=41)	p
Age (years)	68.1±1.48 (66-70)	67.8±1.30 (66-71)	>0.05
Gender			
Male	20	20	>0.05
Female	20	21	>0.05
BMI (kg/m²)	31.8±3.26	32.6±3.43	>0.05
Underweight	0	0	
Normal	1 (%2.5)	0	
Overweight	8 (%20)	2 (%4.9)	
Obese	31 (%77.5)	39 (%95.1)	
SD (years)	15.04±7.01	11.78±6.56	0.025

BMI: Body Mass Index, SD: Symptom Duration

The distribution of patients by their Kellgren-Lawrence stages was shown in table 2. The VAS scores during rest and motion were significantly higher in Group 1 compared to Group 2 (p=0.014 and p=0.018, respectively). There was also no statistically significant difference between the groups according to the WOMAC-stiffness scores (p>0.05). However, statistically significant differences were detected in WOMAC-pain, WOMAC-function and WOMAC-total scores (p<0.001). These scores were significantly higher in the patient group with low vitamin D levels (p=0.001, p<0.001, and p<0.001, respectively) (Table 2).

Table 2. Clinical characteristics of the patients

	Group 1 (n=40)	Group 2 (n=41)	p
Kellgren-Lawrence Stage			
Grade 1	1 (%2.5)	6 (%14.6)	-
Grade 2	27 (%67.5)	28 (%68.3)	-
Grade 3	12 (%30)	7 (%17.1)	-
VAS			
Resting	3 (0-8)	2 (0-5)	0.014
Motion	7 (2-10)	6 (3-9)	0.018
WOMAC-Pain Score	12 (7-18)	8 (2-17)	0.001
WOMAC-Stiffness Score	3 (1-7)	3 (0-8)	>0.05
WOMAC-Functional Score	49 (34-63)	31 (17-43)	0.0001
WOMAC-Total Score	65 (52-81)	44 (26-56)	0.0001

VAS: Visual analog scale, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Compared to Group 2, the peak torque values in Group 1 were significantly lower for average knee flexion and extension strengths for both knees at 60°/sec, and average knee flexion and extension strengths at 180°/sec angular velocities (p<0.001) (Table 3).

Table 3. The mean flexor and extensor peak torque values of the groups at 60 and 180 degrees

	Group 1Nm n=40	Group 2Nm n=41	p
60°/sec EXT PT-right	43.96±15.64	79.27±14.69	<0.001
60°/sec EXT PT-left	40.73±14.44	73.47±17.47	<0.001
60°/sec FLX PT-right	28.18±8.15	41.75±10.63	<0.001
60°/sec FLX PT-left	23.47±10.44	39.89±11.89	<0.001
180°/sec EXT PT-right	28.31±10.96	47.04±12.94	<0.001
180°/sec EXT PT-left	25.92±9.81	45.15±11.78	<0.001
180°/sec FLX PT-right	17.35±8.61	30.62±10.41	<0.001
180°/sec FLX PT-left	16.45±8.97	28.98±10.40	<0.001

Nm: Newton-meter, EXT PT-right: Extension peak torque right knee, EXT PT-left: Extension peak torque left knee, FLX PT-right: Flexion peak torque right knee, FLX PT-left: Flexion peak torque left knee

The arithmetic means of 60 and 180° flexion and extension of the right and left knees were analyzed in multiple stepwise linear regression analysis. According to the results of this analysis, vitamin D deficiency and WOMAC function score were the most important factors affecting the peak torque values of 60 and 180° flexion and extension of the knees (Table 4-7).

Table 4. The results of the multiple regression analysis results using the peak torque value of 60°/sec knee extension as the dependent variable (r=0.719. r²=0.516).

Model	Variable	β	t	p
1	Vitamin D	0.292	2.282	0.025

2	WOMAC Function Score	-1.017	-4.584	0.000
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Table 5. The results of the multiple regression analysis using the peak torque value of 60°/sec knee flexion as the dependent variable (r=0.619. r²=0.383).

Model	Variable	β	t	p
1	Vitamin D	-0.660	-2.052	0.044
2	WOMAC Pain Score	0.277	5.045	0.000
3	Gender	4.447	2.142	0.035

Table 6. The results of the multiple regression analysis using the peak torque value of 180°/sec knee extension as the dependent variable (right r=0.560. r²=0.313. left r=0.583. r²=0.340).

Model	Variable	β	t	P
1	Vitamin D	0.181	1.817	0.073
2	WOMAC Functional	-0.466	-2.698	0.009

Table 7. The results of the multiple regression analysis using the peak torque value of 180°/sec knee flexion as the dependent variable (right r=0.547. r²=0.299. left r=0.568. r²=0.322).

Model	Variables	β	t	p
1	Vitamin D	0.778	2.369	0.020
2	WOMAC Pain Score	-0.750	-2.136	0.036
3	Body Mass Index	0.155	2.612	0.011

DISCUSSION

In this study, the patients with low vitamin D levels were found to have significantly higher pain intensity and disability, and significantly lower muscle strength of the flexor and extensor muscle groups compared to those with normal vitamin D levels.

Vitamin D deficiency is a public health problem concerning all people. However, the level of vitamin D is especially low in the elderly. The most common reasons for the high incidence of vitamin D deficiency in the elderly are decreased exposure to sunlight, reduction in 7-dehydrocholesterol (which is the vitamin D precursor in the skin), a decrease in the number of vitamin D receptors and the turnover of vitamin D to its active form, inadequate consumption of food rich in vitamin D, a decrease in the synthesis capacity of vitamin D in the skin, and reduced absorption of vitamin D from the intestine (17). It was difficult for us to find a sufficient number of elderly people with OA of the knee whose vitamin D levels were within the normal range. Even though Turkey is a Mediterranean country, vitamin D deficiency is especially common in the elderly population. As this may be the effect of the factors mentioned above, we believe that a more covered-up style of dress of elderly people in Turkey may be a significant factor.

Pain is a primary clinic symptom of OA, and as in all other chronic diseases presenting with pain, it occurs as a complicated combination of biological events leading to structural damage, and psychological and social factors (18). It is reported that vitamin D deficiency is another source of pain in OA of the knee. Vitamin D deficiency decreases calcium absorption from the intestines, leading to increased PTH synthesis to keep the blood calcium levels within the normal range. PTH increases the excretion of phosphate, resulting in hypophosphatemia. When there is not enough calcium and phosphate in the circulation, the collagen matrix on the surface of endosteal and periosteal bone cannot mineralize regularly. The irregularly supported collagen matrix becomes hydrated and swells. It causes the pressure to increase in the sensory innervated periosteum, leading to a sensation of pain (19). In a study conducted with African Americans, a relationship was found between vitamin D deficiency and increased pain in OA of the knee (20). In a multicenter retrospective study, Karahan et al. reported that vitamin D deficiency in patients with nonspecific musculoskeletal pain is not associated with the severity and duration of pain (21). Al Faraj et al. reported that intensity and frequency of pain decreased in older people undergoing vitamin D replacement therapy (22). In contrast to studies showing a positive relationship between vitamin D levels and pain, some researchers have found no relationship between the two (23). In the current study, similar to most previous studies, we found higher values of VAS during rest and motion, and higher WOMAC-pain scores in the group with low vitamin D levels compared to the group with normal vitamin D levels.

In the literature, it has been shown that vitamin D deficiency can cause muscle weakness (24). The relationship between serum 25(OH) D levels and strength of the quadriceps muscle has been investigated by many researchers using an isokinetic or isometric dynamometer (25, 26). In many studies, low serum vitamin D levels were found to increase muscle weakness, musculoskeletal pain, and body wagging (17, 23, 25). However, although the relationship between vitamin D levels and muscle strength has been investigated in many different patient populations including the healthy population, athletes, and hemodialysis patients and patients with heart disease (9-11, 13, 27), its effects on muscle strength and functional status has not been explored in detail in the elderly population with OA of the knee. In the current study, average flexor

and extensor muscle strengths were significantly lower in the group with low vitamin D levels compared to the group with normal vitamin D levels. According to the regression analyses, vitamin D deficiency is the most effective factor for the peak torque values of 60° and 180° flexion and extension of the knees. These results show that in patients with OA of the knee, vitamin D deficiency negatively affects the muscle strength.

Vitamin D deficiency is reported to be one of the reasons of metabolically triggered inflammation in osteoarthritis (28). It was shown that a change in 25-(OH)D levels were negatively predicted by baseline body fat, leptin, IL-6, and total cholesterol/high-density lipoprotein (HDL) ratio, suggesting that vitamin D deficiency is involved in the meta-inflammation in patients with OA (29). Vitamin D receptor is expressed in chondrocytes within osteoarthritic cartilage, demonstrating the contributory role of vitamin D in the aberrant behavior of chondrocytes in OA. However, the physiological function of vitamin D on chondrocytes in OA remains obscure. Chen et al. suggested that the ability of vitamin D to potentiate matrix metalloproteinase-13 expression might facilitate cartilage erosion at the site of osteoarthritis (30). In an animal study, Li et al. showed that vitamin D prevented articular cartilage erosion by regulating collagen 2 turnover through TGF-β1 in ovariectomized rats (31). Supporting these findings, vitamin D deficiency was found to be related to the development and worsening of knee OA, including cartilage loss and increased joint space narrowing (32). In an ultrasonographic study, Malas et al. showed that low levels of vitamin D adversely affected the femoral cartilage thickness (33). However, some findings do not support the use of vitamin D supplementation for preventing tibial cartilage loss in patients with knee osteoarthritis (34). In contrast, Lane et al. showed that vitamin D could be used to prevent the progression and incidence of hip and knee OA and Zhang et al. reported vitamin D deficiency to be associated with the progression of knee osteoarthritis (35, 36). In the current study, the mean disease duration in the patient group with low vitamin D levels (Group 1) was significantly longer than Group 2. And also, the patients with Kellgren Lawrence stage 3 were higher in Group 1 (30% to 17%). We think that the patients in the former group probably had low vitamin D levels for a long time; thus, the progression of their knee OA was more serious than the patients with normal vitamin D levels. Therefore, we suggest that low vitamin D levels

may be responsible for the long disease duration. However, this hypothesis should be supported by further studies on human cartilage turnover.

In a study by Sanghi et al., 107 patients with OA of the knee were followed up for a year. The patients were divided into two groups. The first group was given vitamin D supplements and the second was given a placebo. The VAS and WOMAC scores were evaluated. At the end of 12 months, the VAS and WOMAC scores were found to be significantly lower in the group that received vitamin D supplementation compared to the group that received the placebo (37). In a two-year randomized, placebo-controlled, double-blind study conducted with 146 symptomatic patients with OA of the knee, the effects of placebo and oral cholecalciferol on knee pain and cartilage volume loss were investigated. The primary end-point of the study was the WOMAC-pain score and cartilage volume loss visualized by MRI. The secondary end-point of the study was the WOMAC-function score, the thickness of the cartilage, lesions in the bone marrow, and the joint space width evaluated radiologically. After two years of optimal oral cholecalciferol use, no significant decrease was observed in the WOMAC-pain and function scores, and cartilage volume loss in the group that received supplements compared to the placebo group (38). In the current study, we found a statistically significant difference between the groups with and without vitamin D deficiency in terms of the WOMAC-pain, WOMAC-function, and WOMAC-total scores. The scores were significantly higher in the group with low vitamin D levels. These results could be interpreted as that clinically diagnosed vitamin D deficiency increases disability in patients with OA of the knee.

We acknowledge that our study has limitations. We did not evaluate the effects of vitamin D supplementation on radiological progression and muscle strength. The sample sizes could be larger. Study design could be made prospectively which includes consecutive measurements during vitamin D supplementation, rather than cross-sectional. However, there may be ethical debates about this issue. We do not know how long this level was present in patients with low vitamin D Group. Therefore, were vitamin D levels of patients in Group 1 low during their youth? Was it normal? Or for how long did vitamin D levels of patients in Group 2 remained within the normal range. Were there a vitamin D deficiency in previous years?

CONCLUSION

Vitamin D deficiency is common in people over 65 years of age but it is usually overlooked in clinical practice. The low vitamin D levels in the elderly population are associated with chronic pain in the musculoskeletal system and with muscle weakness. We found that vitamin D deficiency is a major risk factor of increased pain, muscle weakness, and disability of elderly patients with knee OA. Therefore, we recommend that these patients be regularly evaluated for vitamin D deficiency. Considering the conflicting reports on the disease-modifying role of vitamin D, further long-term studies are needed to evaluate the effects of vitamin D on cartilage metabolism, the radiological progression of OA, and clinical features of OA patients.

Etik: Bu çalışmanın etik kurulu alınmıştır.

Ethics committee approval had been taken.

Yazar katkı durumu; Çalışmanın konsepti; SEA, BDÇ dizaynı; SEA, BDÇ Literatür taraması; SEA, HG, verilerin toplanması ve işlenmesi; SEA istatistik; SEA, BDÇ, ES, HG yazım aşaması; SEA, BDÇ, ES, HG

Author contribution status; The concept of the study; SEA, BDÇ design; SEA, BDÇ literature review; SEA, HG, collecting and processing data; SEA statistics; SEA, BDÇ, ES, HG writing phase; SEA, BDÇ, ES, HG

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