The Relation Between Vitamin D, Severity of Knee Osteoarthritis and Inflammatory Parameters

D Vitamini, Diz Osteoartriti Şiddeti ve Enflamatuvar Belirteçler Arasındaki İlişki

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Abstract

Objective: The pathogenesis and progression of osteoarthritis (OA) are related to low-grade inflammation. Objectives were conducted; first to investigate whether neutrophil-to-lymphocyte, platelet-to-lymphocyte ratios are appropriate parameters to determine low-grade inflammation in knee OA. The second objective was to evaluate whether vitamin-D deficiency contributes to the severity of OA and these inflammatory parameters as well.

Materials and Methods: 623 patients with knee-pain were evaluated retrospectively, 136 patients with knee OA were included. 25-hydroxyvitamin D, complete-blood count, C-reactive protein, erythrocyte-sedimentation rate, knee radiographs (Kellgren-Lawrance scale) was recorded.

Results: "Vitamin-D deficiency" was detected in 52.2% of all patients (<20 ng/mL). Blood parameters and severity of knee OA was found similar between patients with "25-hidroxyvitamin D <20 nanogramme/mililiters" and "≥20 nanogramme/mililiters." 59.5% of patients had "mild OA," 40.4% of patients had "moderate-to-severe OA." All parameters were found similar between these two groups, only age was found significantly higher (p<0.001) in patients "moderate-to-severe OA."

Conclusion: Neutrophil to lymphocyte, platelet to lymphocyte ratios are not found as appropriate parameters in determining low-grade-inflammation in knee OA; moreover there were found no relation between vitamin-D deficiency and both radiological severity and inflammation parameters in knee OA.

Keywords: Inflammation, knee osteoarthritis, vitamin D

Öz

Amaç: Osteoartritin (OA) patogenezi ve progresyonunun düşük dereceli enflamasyon ile ilişkili olduğu bilinmektedir. Bu çalışmanın amacı öncelikle nötrofil/lenfosit oranı ve platelet/lenfosit oranlarının OA'daki düşük düzey enflamasyonunu belirlemede uygun parametreler olup olmadığını araştırmaktır. İkincil amaç da D vitamini eksikliğinin, OA'nın radyolojik şiddetine ve enflamatuvar parametrelere katkıda bulunup bulunmadığını araştırmaktır.

Gereç ve Yöntem: Diz ağrısı ile başvuran toplam 623 hasta dosyası incelenerek, çalışmaya dahil edilme kriterlerine uyan, 136 diz osteoartritli hasta dosyası çalışmaya dahil edilmiştir. 25-hidroksivitamin D, tam-kan sayımı, eritrosit sedimentasyon-hızı, C-reaktif protein ve diz radyografilerindeki Kellgren-Lawrance evreleri kayıt edilmiştir.

Bulgular: Çalışmamıza alınan hastaların %52,2'sinde D vitamini eksikliği saptanmıştır (<20 ng/mL). D vitamini değeri <20 ng/mL ve ≥20 ng/mL olan hastalar arasında ne OA şiddeti ne de enflamasyon parametreleri açısından fark saptanmamıştır. Radyografik osteoartrit hastaların %59,5'inde hafif düzeyde, %40,4'ünde ise orta-şiddetli düzeyde saptanmıştır. Yaş açısından değerlendirildiğinde ise, orta-şiddetli OA olan hastaların yaşı, istatistiksel olarak hafif OA'sı mevcut olan hastalara göre fazla bulunmuştur (p<0,001). Yaş dışındaki parametreler açısından, hafif ve orta-şiddetli OA'sı olan hastalarda fark saptanmamıştır.

Sonuç: Bu çalışmada, nötrofil/lenfosit oranı ve platelet/lenfosit oranının, diz osteoartritindeki düşük dereceli enflamasyonu belirlemede yetersiz olduğu sonucuna ulaşılmıştır. Ayrıca D vitamini eksikliğinin, radyolojik olarak OA şiddeti ve enflamatuvar parametreler üzerine etkisi saptanmamıştır.

Anahtar kelimeler: Enflamasyon, diz osteoartriti, vitamin D

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Introduction

There is evidence that the progression, also the pathogenesis of osteoarthritis (OA) has a relationship with low-grade-inflammation (1). Inflammation in synovium; histologically, synovitis involved infiltration of inflammatory cells, such as mononuclear cells (2) inflammatory mediators and cytokines resulting with degenerative changes in cartilage and often contributing to radiographic damage (3) in knee OA (4-6).

It is important to prove the inflammation of patients with knee OA in routine clinical practice to know the progression. In recent studies, many inflammatory parameters were investigated in knee OA and there are conflicting results. Creactive protein which a marker of inflammation, is predictive of the progression of OA (7). And also a simple ratio of neutrophil to lymphocyte (NLR) and platelet to lymphocyte ratios (PLR) are easily measured from complete blood count, are inexpensive systemic markers for subclinical low grade inflammation in many circumstances, In inflammation and stress responses, neutrophil counts increases and lymhocyte counts decreases. On the other hand many inflammatory mediators such as IL-6, decreases the level of platelet by stimulating platelet production (8). Furthermore platelet stimulation takes place giving way to neutrophil stimulation. In inflammation, both platelet and neutrophil levels increase, lymphocyte count decreases in peripheral blood. Higher blood NLR and PLR was reported to be related with many rheumatological diseases (9,10). Also in knee OA, some studies found their levels elevated (11,12) conversely in some studies they were not found elevated (13). On the other hand, a higher cartilage loss was reported with vitamin-D insufficiency as well [25-hydroxyvitamin D (25-(OH)D)<20 nanogramme/mililiters], normal levels of vitamin D is important for both musculoskeletal system (14,15) also for other systems (16,17). However, some conşicting studies reported that vitamin D insufficiency is not associated with knee-OA (18-21). It is known that, vitamin D modulates inşammatory cytokines (22) which contribute to the pathological process of knee-OA. Besides that, vitamin D deficiency has a relationship with elevated C-reactive protein (CRP) concentrations (23) and NLR, PLR (24) in other diseases. Considering the effects of vitamin D on inflammation, it is expected that vitamin D deficiency may contribute to OA progression.

In the above studies, the effect of vitamin D on either OA severity or inflammatory parameters were investigated. This study was designed to determine the effect of vitamin D on both OA severity and inflammatory parameters, also to investigate whether NLR, PLR are appropriate parameters in routine clinical practise to determine low-grade inflammation in knee OA.

Materials and Methods

This is a retrospective investigation of our outpatient clinic patients with knee ache between January 2019 and May 2020 by searching their records. The datas of 623 patients with knee ache were reviewed for gender, age, 25-(OH)D levels, complete blood count and knee radiographs.

Inclusion criteria were as follows: aged between 40-80 years with records of 25-(OH)D levels, complete blood count and knee graphies. Exclusion criteria were as follows: patients with knee surgery, total knee arthroplasty, rheumatoid-factor and antinuclear antibodies positivity and rheumatological diseases, hematological diseases, infectious diseases, bone/soft tissue tumors.

Knee radiographs were interpreted by two physical therapy and rehabilitation specialists for Kellgren-Lawrance (K-L) scale (25): grade 0- normal, grade 1- doubtful narrowing in the joint space, possible osteophyte, grade 2- definite osteophyte, possible narrowing in the joint space, grade 3- moderate osteophytes, definite norrowing in the joint space, some sclerosis, grade 4- marked narrowing in the joint space, severe sclerosis and definite bone ends deformity.

The level of 25-(OH)D, the count of platelet, neutrophil and lymphocyte, the NLR and PLR, mean platelet volume, erythrocyte sedimentation rate (ESR), CRP records were taken from blood tests. Serum 25-(OH)D values; 0-19.99 ng/mL (50 nmol/mL) was defined as vitamin D deficiency (26).

The study was carried out with the approval of the Council of Ethics of the Eskişehir Osmangazi University Non-Invasive Clinical Researches Ethics Committee (decision no: 23, date: 11.08.2020).

Statistical Analysis

The distribution of each continuous variable was tested with Shapiro-Wilk test and descriptive statistics were mean ± standard deviation or median (25-75%). Normally distributed variables were performed with independent samples t-test and non-normally distributed variables were performed using the Mann-Whitney U test. The categorical variables (i.e. presence gender) were evaluated with chi-square tests and were presented as numbers and percentages. A p-value <0.05 was considered as statistical significant. All analyses were performed using the SPSS version 22.0 software (SPSS Inc., Chicago, IL, USA).

Results

One hundred and thirty six (125 female, 11 male) met the criteria. Mean age was 60.85±10.02.

Eighty one (59.5%) patients had mild OA, 55 (40.4%) patients had moderate to severe OA. Only age was found significantly higher in patients with moderate to severe OA (p<0.001). Other parameters were similar between patients with mild OA and moderate to severe OA (Table 1). 52.2% of all patients had vitamin D deficiency (<20 ng/mL). All parameters found similar between patients with 25-(OH)D<20 nanogramme/mililiters and ≥20 nanogramme/mililiters (Table 2).

Discussion

According to results of present study, inflammatory parameters; NLR, CRP and ESR values were found higher in moderate to severe OA patients than mild OA patients however the

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Table 1. Demographic characteristics and laboratory findings of knee osteoarthritis patients according to knee osteoarthritis severity			
	Mild osteoarthritis (K-L grade 1-2) (n=81)	**Moderate to severe osteoarthritis (K-L grade 3-4) (n=55)**	**p-value**
Age*	58.03±9.53	65.0±9.33	p<0.001
Female/male n (%)	74 (91.3%)/7 (7.6%)	51 (92.7%)/4 (7.2%)	0.775
Leucocyte count*	7.41±1.79	7.71±2.16	0.379
Platelet count**	261 (224-312)	244 (211-291)	0.232
NLR*	1.81±0.67	1.94±0.80	0.320
PLR**	111 (91-137)	109 (90-124)	0.373
MPV**	7.67 (6.69-8.77)	7.95 (7.03-8.96)	0.370
ESR**	13 (6-22)	14 (9-22)	0.259
CRP*	2.60±2.38	3.68±4.24	0.138
25-hidroxyvitamin D*	22.58±19.78	19.39±10.62	0.276
CRP: C- reactive protein, ESR: Erythrocyte sedimentation rate, K-L: Kellgren Lawrance, NLR: Neutrophil to lymphocyte ratio, MPV: Mean platelet volume, PLR: Platelet to lymphocyte ratio, *mean ± standard deviation **median (25-75%)			

Table 2. Age and laboratory findings of knee osteoarthritis patients according to 25-hidroxyvitamin D levels			
	25-hidroxyvitamin D <20 ng/mL (n=71)	**25-hidroxyvitamin D ≥20 ng/mL (n=65)**	**p-value**
Age*	59.87±9.70	61.92±10.32	0.235
Leucocyte count*	7.45±1.59	7.62±2.28	0.608
Platelet count**	244 (216-309)	266 (225-299)	0.226
NLR*	1.82±0.73	1.91±0.73	0.489
PLR**	105 (89-125)	112 (96-152)	0.139
MPV**	7.81 (6.73-8.93)	7.68 (6.82-8.73)	0.665
ESR**	14 (8-22)	15 (6-22)	0.664
CRP*	2.59±2.84	3.59±3.74	0.166
CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, NLR: Neutrophil to lymphocyte ratio, MPV: Mean platelet volume PLR: Platelet to lymphocyte ratio, *mean ± standard deviation, **median (25-75%)			

difference was not significant. Hematologic parameters (NLR, PLR) are accepted as inflammation parameters in a lot systemic inflammatory diseases (9,27). There are conflicting results about these inflammatory parameters in knee OA. Different from our study, Shi et al. (11) found PLR in knee OA importantly upper than healthy people. In another study which compares patients with or without OA: CRP, ESH, PLR, NLR levels were reported as high in knee OA group (12). Methodologies are different due to the lack of healthy people in our research, osteoartritis is an inflammatory disease, so inflammatory parameters are expected to be higher than healthy people. In addition, there are some studies in which patient groups were designed according to K-L Grades. Similar to our study results, Atar and Aşkın (13) compared patients K-L grade 2 and 3, and found no significant difference in CRP, ESH, NLR, PLR. Likewise, in other two studies, no relation was reported between PLR and K-L grades (11,28). Also in a review CRP was reported not to be associated with

radiological progression (29). Besides there are studies with different results from ours. Taşoğlu et al. (30) found blood NLR levels higher in K-L Grade 4 group when compared with K-L grade 1-3 group. Similar to Taşoğlu et al's. (30) study, Koca et al. (28) found the level of serum white blood cells and NLR to be higher in advanced OA (K-L grade 3-4) than mild OA (K-L grade 1-2). Considering the evidence of inflammation on OA progression (1), the absence of a significant difference in our study can be explained by the fact that inflammation is limited to local area and NLR, PLR are not appropriate parameters in determining low-grade inflammatory processes in knee OA.

In our study, the vitamin-D deficiency ratio was found to be 52.2% in patients. Our rates were similar to previous studies with knee OA in Turkey. A study reported the vitamin-D deficiency ratio as 57.5% of 99 patients with knee OA (31), also another study reported as 59.09% (32). The rates of other countries were different from our study. In Tasmanian, it was found as

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45% in knee OA (19). In Kuwait, the rate was reported as 92.9% (20). Majority of our patients were women, although Turkey and Kuwait are sunny countries, the traditional clothes may cause inadequate skin exposure to sunlight.

Vitamin D has many metabolic effects in musculoskeletal system such as calcium homeostasis, in addition, the immunomodulating properties were investigated in recent years (33). Active vitamin D in the body, reduces the production of proinflammatory cytokines and chemokines (34) which plays a great role in OA pathogenesis and progression. There are many investigations on immunmodulating result of vitamin-D, only a few studies were found which showed the relation between vitamin-D and inflammatory processes in knee OA. Zheng et al. (35) reported vitamin D intake over 2 years did not change serum levels of inflammation parameters such as CRP in knee OA with insufficient vitamin-D levels. Similar to our study result, a study found similar levels in CRP, interleukins, TNF-α in all deficient, insufficient and sufficient vitamin D groups in knee OA (36). Also similar to our study results, Altaş and Tosun (37) showed no relation between vitamin D and both NLR and PLR. There is a need for different measurement methods sensitive than CRP, NLR and PLR to show the consequences of vitamin D treatment on inflammatory processes in knee OA.

Immunomodulatory properties are affected with vitamin D insufficiency in knee OA, so OA is expected to progress severe. However in our investigation, no relation was found between vitamin-D deficiency and radiological severity. There are contradictory results about vitamin D insufficiency and severity of OA in literature. Different from our study, in the Framingham study (14), knees of patients with vitamin D insufficiency (<20 nanogramme/mililiters) showed a slightly increased risk of joint space loss than patients without insufficiency (14). Similar to our study, Al-Jarallah et al. (20) showed that one measurement of vitamin D in blood was not related with the radiological progression. Since the development of radiological severity of OA will take many years, the relation between one time measurement of 25-(OH)D and radiological severity may not be found. We believe, if severity of OA was evaluated with long period measurements instead of one measurement of 25-(OH) D, the relation could be found.

Not being a longitudinal follow-up study due to its retrospective design is one of the limitations. Our study investigated the severity and inflammation with the level of vitamin D at only that time, however there is need for studies evaluating inflammation and both radiological and clinical severity before and after vitamin D treatment with sensitive markers. The other limitation was the lack of healthy control group.

Conclusion

NLR, PLR are not found as appropriate parameters in determining low-grade inflammation in knee OA moreover there was found no effect of vitamin D on radiological severity and inflammation parameters in knee OA.

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