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RESEARCH

Serum leukocyte cell-derived chemotaxin-2 (Lect-2) levels in osteoarthritis patients

Osteoartrit hastalarında serum lökosit hücre kaynaklı kemotaksin-2 (Lect-2) düzeyleri

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Abstract

Purpose: An association between the complimentary system and osteoarthritis is becoming more apparent. Lect-2 protein acts as a regulator of immunological and inflammatory responses. This study aims to determine the levels of leukocyte cell-derived chemotaxin-2 (Lect-2) in patients with osteoarthritis.

Materials and Methods: The study included 38 osteoarthritis patients and 36 healthy controls. ESR, WBC, serum CRP and Lect-2 levels were measured both in patients and controls.

Results: ESR and serum CRP levels were significantly higher in patients compared to controls. The mean Lect-2 level in osteoarthritis patients (14.2±4.8 ng/mL) was significantly lower compared to the healthy control group (56.3±20.7 ng/mL). ROC analysis revealed that–serum LECT-2 level was a significant parameter in determining patients from healthy controls. Cut off value was ≤24.8 ng/mL with a high AUC (0.990).

Conclusion: The significant reduction in Lect-2 levels in osteoarthritis patients suggests its potential role in disease pathogenesis. This finding may contribute to understanding the immunological aspects of osteoarthritis and could potentially serve as a biomarker for disease progression. Further studies with larger patient populations are needed to validate these findings and explore the therapeutic implications of Lect-2 in osteoarthritis management.

Keywords:. Immune system, Lect-2, osteoarthritis

Öz

Amaç: Komplemantar sistem ile osteoartrit arasındaki ilişki giderek daha belirgin hale gelmektedir. Lect-2 proteini, immünolojik ve inflamatuar yanıtların düzenleyicisi olarak görev yapar. Bu çalışmanın amacı, osteoartrit hastalarında lökosit hücre kaynaklı kemotaksin-2 (Lect-2) düzeylerini belirlemektir.

Gereç ve Yöntem: Çalışmaya 38 osteoartrit hastası ve 36 sağlıklı kontrol grubu dahil edildi. Hasta ve kontrol grubunda sedimentasyon, beyaz küre, serum CRP ve Lect-2 düzeyleri ölçüldü.

Bulgular: Hastalarda ESR ve serum CRP düzeyleri kontrol grubuyla karşılaştırıldığında anlamlı derecede yüksekti. Osteoartrit hastalarında ortalama Lect-2 düzeyi (14.2±4.8 ng/mL) sağlıklı kontrol grubuna (56.3±20.7 ng/mL) göre anlamlı derecede düşük bulundu. ROC analizi serum LECT-2 düzeyinin hasta ile sağlıklı ayrımı yapmada önemli bir parametre olduğunu ortaya koydu. Kesim değeri yüksek AUC (0,990) ile ≤24,8 ng/mL idi.

Sonuç: Osteoartrit hastalarında Lect-2 düzeylerinin belirgin şekilde düşük olması, bu molekülün hastalık patogenezinde potansiyel rolünü göstermektedir. Bu bulgu, osteoartritin immünolojik yönlerinin anlaşılmasına katkı sağlayabilir ve hastalık progresyonunda bir biyobelirteç olarak kullanılabilir. Bu bulguların doğrulanması ve Lect-2'nin osteoartrit tedavisindeki olası rolünün araştırılması için daha geniş hasta popülasyonlarıyla yapılacak ileri çalışmalara ihtiyaç vardır.

Anahtar kelimeler: İmmün sistem, Lect-2, osteoartrit.

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INTRODUCTION

Osteoarthritis (OA) is a prevalent degenerative joint condition widely observed. Such pathological progression can be recognized by the deterioration of the joint cortex. Patients might suffer from subchondral sclerosis, cyst formation, and osteophyte development[1].

The etiology of OA is multi-factorial, involving joint injury, obesity, aging, and heredity, which in turn lead to complex pathological changes including progressive loss and destruction of articular cartilage, thickening of the subchondral bone, formation of osteophytes, variable degrees of synovial inflammation, degeneration of ligaments and menisci, and hypertrophy of the joint capsule[2]. Osteoarthritis (OA), clinically characterized by pain, stiffness, joint effusion, and loss of joint function/motivity, is a disease that may be associated with initial genetic, structural, and biomechanical risk factors. The pathological mechanism occurs due to the gradual loss of hyaluronic tissue[3].

Osteoarthritis is characterized by altering the healthy homeostatic state toward a catabolic state, where inflammation plays a crucial role. Chronic low-grade inflammation contributes to disease development and progression, with conventional inflammatory factors such as IL-1β and TNF-α, along with chemokines and innate immune signals including damage-associated molecular patterns (DAMPs), alarmins (S100A8 and S100A9), and complement, all involved in OA pathogenesis[4].

. The fundamental cellular hallmarks of OA pathology include hypertrophic differentiation of chondrocytes, as well as the activation of pro-inflammatory signaling pathways that promote cell death[5]. Nevertheless, there has been limited understanding of the involvement of cellular glycophenotypes in the initiation and progression of OA. Researchers have identified the effect of the pro-inflammatory cytokines interleukin-1β and tumor necrosis factor-α on the glycan composition of chondrocytes[6].

There is growing evidence indicating a connection between the complementary system and OA. Firstly, the levels of C4d and C3bBbP have been significantly elevated, ranging from 2 to 34 times higher, in individuals with OA, rheumatoid arthritis (RA), and pyrophosphate arthritis (PPA) compared to the control group's patients. C3, C4, and Fb have been found in various tissues in the joints of OA patients, and in vitro, cultures have demonstrated that chondrocytes can produce C3a and C5a[7].

In an OA mice model, an abundance of macrophages is essential for the onset of inflammation. Chondrocytes harvested from animals deficient in C5 have exhibited diminished inflammation compared to the control group. Similarly, through metabolic reprogramming of synovial fibroblasts, C3 and C3a can stimulate the development of local inflammation in the tissue, and the breakdown of C3 can minimize osteoarthritis areas and reduce inflammatory damage[7].

Leucocyte cell-derived chemotaxin-2 (Lect-2), which originates from leukocyte cells, is a protein that supports many physiological roles. It is expressed in human liver cells (hepatocytes) and delivered into the bloodstream[8]. Lect-2 exhibits chemokine and hepatocine properties, similar to hormones[9].

Along with the research, it has been established that Lect-2 regulates the migration of neutrophilic cells and plays a part in the development of renal and hepatic amyloid lesions[9]. Research has also demonstrated that Lect-2 is a significant factor in other pathophysiological processes, including sepsis, hepatitis, arthritis, and hepatocarcinoma. It acts as a regulator of immunological and inflammatory responses. Lect-2 also contributes to metabolic illnesses such as obesity, diabetes, and non-alcoholic fatty liver disease[8,9].

Leucocyte cell-derived chemotaxin-2 (Lect-2) levels are elevated in individuals with autoimmune disorders and OA. The effectiveness of Lect-2 in assessing the severity of OA is notable since it indicates considerably elevated levels compared to persons without the disease[9,10].

Lectins are proteins that can attach to particular sugar compounds on cell surfaces to affect immunological responses, adhesion, and cell signaling. Lectins have key roles in stimulating immunological responses, particularly in multicellular organisms[11].

Emerging studies have identified inflammatory mediators, including cytokines and oxidative stress, as key players in osteoarthritis (OA) progression, yet the role of Lect-2 in OA remains underexplored, despite its suggested involvement in immune regulation[12].

Our study hypothesizes that Lect-2 levels may be altered in OA patients compared to healthy individuals, potentially serving as a novel biomarker

for disease progression. This investigation aims to fill an important gap in the literature by providing the first comprehensive analysis of serum Lect-2 levels in OA patients and their potential correlation with disease severity.

MATERIALS AND METHODS

Our research is a prospective study conducted at Erzurum Ataturk University Faculty of Medicine Physical Therapy and Rehabilitation Polyclinic between January 2023 and December 2023. All clinical evaluations were performed by a specialist physician with at least 5 years of experience in rheumatology. Laboratory analyses were conducted at the Biochemistry Laboratory of the Faculty of Pharmacy.

Sample

Based on previous similar studies, the sample size was calculated using G*Power 3.1.9.2 software. With an effect size of 0.8 (large), α error of 0.05, and power of 0.91, the minimum required sample size was determined to be 36 participants per group. Initially, 45 OA patients and 42 healthy controls were approached. After applying exclusion criteria, 38 OA patients and 36 healthy controls were included in the final analysis. Seven patients were excluded due to: concurrent autoimmune disease (n=2), recent sepsis (n=1), active cancer treatment (n=1), and declined participation (n=3). Six controls were excluded due to: newly diagnosed chronic disease (n=2) and incomplete data (n=4). Inclusion criteria were; being diagnosed with OA by ACR criteria, and aged between 18-80 years. Exclusion criteria were; having sepsis, autoimmune diseases, cancer, and rheumatoid arthrisis. Healthy controls were recruited from healthy volunteers of hospital staff who do not have acute or chronic diseases. They were age- and gender-matched with the patient group and underwent comprehensive health screening to ensure they met the inclusion criteria.

Procedure

The study acquired ethical board permission from the Ethics Board for Scientific Research of the Medical Faculty of the University of Ataturk (Decision No. 2024/247, dated 15.01.2024). Written informed consent was obtained from all participants.

Blood samples were collected from all participants between 8:00-10:00 AM after overnight fasting. For each participant, 5 mL of venous blood was drawn into serum separator tubes. Samples were allowed to clot for 30 minutes at room temperature, then centrifuged at 3000 rpm for 15 minutes. These serums were stored at -20ºC until analysis. During analysis, samples were slowly warmed to room temperature. Lectin levels were examined using an ELISA kit following the manufacturer's protocol with double control.

Statistical analysis

Statistical analysis was performed using SPSS version 25.0 (demo version) and GrapPad 10.2.3 (demo version). Normality was assessed using the Kolmogorov-Smirnov test. Continuous variables were presented as mean ± standard deviation and categorical variables as frequencies and percentages. Between-group comparisons were made using independent t-tests for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. The Chi-square test was used for categorical variables. Receiver operating characteristic (ROC) analyses were performed in the MedCalc 20.218 (demo version) program to define the role of LECT-2 in determining osteoarthritis. Statistical significance was set at $p<0.05$.

RESULTS

In this prospective study of 38 OA patients and 36 healthy controls, our demographic analysis revealed comparable age distributions between the OA group (57.7±8.3 years) and controls (54.3±9.5 years), with no significant gender disparity. However, OA patients demonstrated significantly higher BMI values (28.4±4.2 kg/m²) compared to controls (25.1±3.8 kg/m²). Notably, OA patients showed a higher prevalence of comorbidities, particularly hypertension (31.6%) and obesity (26.3%), suggesting potential metabolic implications in disease progression (Table 1).

Clinical assessment of OA patients revealed predominant knee involvement (63.2%), followed by hip (21.1%) and hand (15.7%) joint manifestations. Pain severity evaluation using the Visual Analog Scale indicated that the majority of patients (57.9%) experienced moderate pain intensity, while equal proportions (21.1% each) reported mild and severe pain levels. These findings highlight the significant impact of OA on patient quality of life and functional status (Table 2).

Table 1. Demographic and clinical characteristics of study participants

Characteristic	OA Group (n=38)	Control Group (n=36)	P-value
Age (years)	57.7±8.3	54.3±9.5	0.104
Gender (M/F), n (%)	16(42.1)/22(57.9)	14(38.9)/22(61.1)	0.964
BMI (kg/m²)	28.4±4.2	25.1±3.8	0.002*
Disease Duration (years)	4.8±2.6	-	-
Comorbidities, n (%)			
- Hypertension	12 (31.6)	4 (11.1)	0.033*
- Diabetes	8 (21.1)	3 (8.3)	0.124
- Obesity	10 (26.3)	4 (11.1)	0.047*

*Statistically significant ($p<0.05$)

Table 2. Clinical features of OA patients (n=38)

Clinical Feature	n (%)
Affected Joint	
- Knee	24 (63.2)
- Hip	8 (21.1)
- Hand	6 (15.7)
Pain Severity (VAS)	
- Mild (1-3)	8 (21.1)
- Moderate (4-7)	22 (57.9)
- Severe (8-10)	8 (21.1)

Table 3. Comparison of laboratory parameters between groups

Parameter	OA Group (n=38)	Control Group (n=36)	P-value
CRP (mg/L)	5.8±3.2	2.3±1.4	0.003*
ESR (mm/h)	22.4±11.6	12.8±6.4	0.008*
WBC ($\times 10^9$/L)	7.8±2.1	7.2±1.9	0.214

*Statistically significant ($p<0.05$), VAS: Visual Analog Scale, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, WBC: White blood cell count

Table 4. Correlation Analysis of Lect-2 Levels with Clinical Parameters in OA Group

Parameter	Correlation Coefficient (r)	P-value
Age	-0.245	0.138
Disease Duration	-0.412	0.010*
BMI	-0.324	0.047*
Pain Score (VAS)	-0.386	0.017*
CRP	-0.368	0.023*
ESR	-0.298	0.069

*Statistically significant ($p<0.05$)

Table 5. ROC analysis results of LECT-2 in determining ostearthritis

Variable	Cut-off value	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	AUC	P Value
LECT-2	≤24.8	100.0	97.2	97.4	-	0.990	<0.001

Laboratory analyses demonstrated markedly reduced Lect-2 levels in OA patients (14.2±4.8 ng/mL) compared to healthy controls (56.3±20.7 ng/mL, $p<0.0001$) (Figure 1). This substantial difference was accompanied by significantly elevated inflammatory markers in the OA group, including CRP (5.8±3.2 vs 2.3±1.4 mg/L, $p=0.003$) and ESR (22.4±11.6 vs 12.8±6.4 mm/h, $p=0.008$). Interestingly, white blood cell counts remained comparable between groups, suggesting a specific rather than systemic

inflammatory response (Table 3). Correlation analyses revealed significant negative associations between Lect-2 levels and several clinical parameters in OA patients. Most notably, strong negative correlations were observed with disease duration (r=-0.412, p=0.010) and pain scores (r=-0.386, p=0.017). Additionally, Lect-2 levels showed inverse relationships with BMI (r=-0.324, p=0.047) and CRP levels (r=-0.368, p=0.023), suggesting potential links between Lect-2, inflammation, and metabolic factors in OA pathogenesis. The correlation with ESR, while negative, did not reach statistical significance (r=-0.298, p=0.069) (Table 4).

The results of ROC analysis of LECT-2 in demonstrating the distinction of patients from healthy controls are shown in Table 5 and Figure 2. It was shown that serum LECT-2 level was a significant parameter in determining patients from healthy controls. Cut off value was ≤24.8 with a high AUC (0.990).

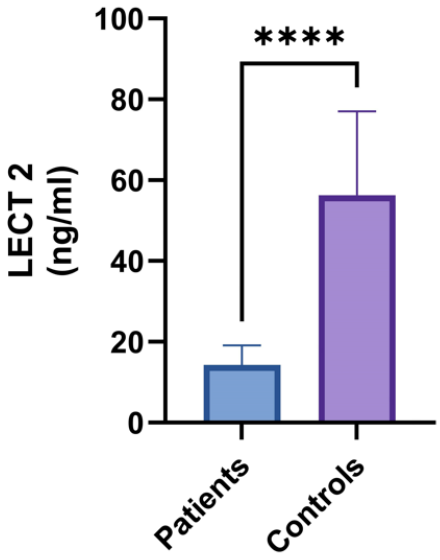

Figure 1. LECT-2 results of patients and healthy controls (**: P<0.0001).**

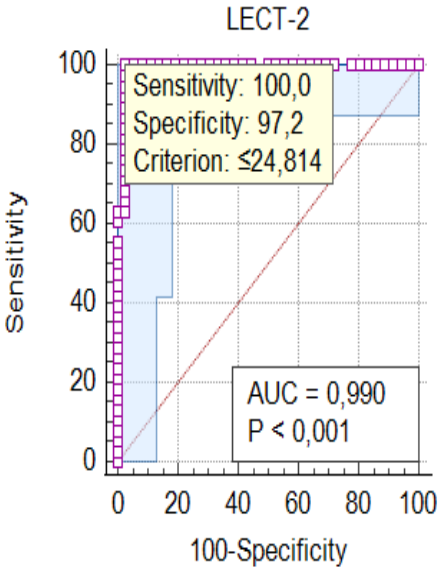

Figure 2. ROC curve analysis of LECT-2 for determining osteoarthritis

DISCUSSION

Our findings add to the growing body of evidence regarding Lect-2's role in joint inflammation. We report significant lower serum Lect-2 levels in osteoarthritis patients compared to healthy controls. There is growing evidence that osteoarthritis is associated with the complement system including lectin pathway[13,14].

During an experiment conducted on mice with collagen type II-induced rheumatoid arthritis, it was shown that the levels of Lect-2 were significantly reduced in the diseased animals. An enormous increase in the concentrations of IL-1β and IL-6, known to be involved with arthritis, was observed at this low level[15]. This relationship between reduced Lect-2 levels and increased inflammatory markers aligns with our observations in human subjects.

In our study population, the interplay between comorbidities and OA presented notable findings. Several different disorders may be considered risk factors for OA. Chronic disorders, such as diabetes, obesity, high cholesterol, and hypertension, have been seen to impact the shape of the snore and the amount of synovial fluid present in the joint snores. Such conditions also appeared to influence the death rate of people suffering from OA[16]. Furthermore, lipid metabolic problems might result in compromised immunological homeostasis[17].

Research has demonstrated variations in Lect-2 levels, which are associated with abnormalities in obesity, diabetes, and lipid metabolism[18]. Our data particularly highlighted this relationship, as patients with comorbidities showed distinct variations in Lect-2 levels compared to those without metabolic disorders. Considering all of these factors, it is important to assess OA with any coexisting conditions. That is one of the limitations that we have to take into account.

Age-related variations in Lect-2 expression represent an important aspect of our investigation. The study found that Lect-2 levels have been somewhat diminished in individuals aged 65 and above, particularly as compared to adults[19]. While our sample size limited age-stratified analyses, this research team neglected to assess the influence of age due to the small specimen quantity. In addition, our study has revealed that there has been no significant disparity in age and gender between individuals in the control group and those diagnosed with OA. This demographic matching strengthens our findings regarding Lect-2 differences between groups, though future studies with larger age-stratified cohorts may reveal additional insights.

Although the exact pathophysiology of the degenerative process of OA is not fully known, it is known that low-grade inflammation causes an imbalance between anabolic and katabolic activities. The formation and progression of osteoarthritis are significantly influenced by the intricate network of cytokines that control these functions and cell communication[20]. Understanding the immune-modulatory role of Lect-2 provides crucial context for our findings in OA patients.

In our study, the inflammatory state was demonstrated with high CRP and ESR levels in patients compared to controls. The relationship between inflammatory markers and Lect-2 levels observed in our study are in line with results of studies conducted in other inflammatory conditions. A subsequent study carried out on participants who had intense sepsis therapy revealed that Lect-2 levels were notably reduced compared to those of healthy individuals on the day of discharge and Lect-2. Patients exhibited a reduction in CRP, procalcitonin, immature WBC total count, and neutrophil count, accompanied by a variation in Lect-2 levels. Nevertheless, IL-6 exhibited the most significant reduction in concentration among the cytokines, but the variations in IL-8 and IL-10 concentrations differed on an individual basis[15]. A research conducted in Japan revealed a significant decrease in Lect-2 levels among sepsis patients compared to those who were in good condition. The study revealed that Lect-2 levels, initially at a low level, showed a little increase with intense maintenance therapy, but this increase was not statistically significant. The study also indicated a correlation between increasing levels of C-reactive protein (CRP) and decreasing levels of Lect-2[14]. Our findings demonstrate similar inverse correlations between CRP and Lect-2 levels in OA patients, suggesting a common inflammatory pathway.

The proteomic aspects of OA pathogenesis provide an important context for interpreting our Lect-2 findings. Hsueh et al. suggested that proteomics displayed notable variation within individuals with OA[21]. Based on this compilation of data, the proteomics measurements for each tissue in the joint region vary between a healthy state and the presence of OA. While our study focused specifically on serum Lect-2 levels, future research combining proteomic analysis with Lect-2 measurements could provide deeper insights into the molecular pathways involved. Insufficient resources and limited time for immune response and proteomic investigations provide a restriction to our detailed research progress.

Comorbidities in our study population warrant careful consideration when interpreting Lect-2 measurements. Some chronic diseases may affect the amount and the quality of joint synovial fluid. In our study, there were 3 patients diagnosed with diabetes mellitus and 4 patients diagnosed with obesity, and the other patients in the patient group had no known chronic diseases. Although we controlled for these factors in our analysis, it was thought that diabetes mellitus and obesity, which are chronic diseases accompanying the patients, may also affect Lect-2 levels. Future studies with larger cohorts and stratification by comorbidity status could help elucidate the specific impact of these conditions on Lect-2 expression in OA patients.

Several limitations should be considered in our study, including the relatively small sample size, single-center design, and cross-sectional nature which prevents assessment of temporal changes in Lect-2 levels. The presence of comorbidities in some patients, such as diabetes mellitus (n=3) and obesity (n=4), may have influenced Lect-2 levels independently of OA. Additionally, the lack of radiological grading correlation and synovial fluid

Lect-2 measurements represents areas for future research to better understand the relationship between Lect-2 and OA pathogenesis.

Future Directions of the study may be summarized as follows: The observations made about Lect-2 in OA pose many useful scenarios for further research. If cohort studies in larger populations are conducted, it may be possible to determine whether or not lect-2 levels may be useful in predicting the progression of OA. Also, measuring, besides serum markers, synovial fluid levels of Lect-2 would add knowledge about localized versus systemic changes. New Lect-2 lowering drugs may be developed from studies looking at the effect of different OA treatment schemes on lect-2 levels. Moreover, patients affected with other diseases have different comorbidity profiles which according to studies exploring relationships among Lect-2 and other inflammatory mediators in OA, might help making sense of this mediator in disease development. Proteomic studies in OA combined with studies of the lect-2 pathway would make it possible to find new treatments for OA.

Our research shows that OA patients have significantly lower levels of Chemotaxin 2 (Lect-2) which appears to be inversely associated with inflammatory markers as well as clinical parameters when compared with healthy controls. Confirming its potential importance in OA pathogenesis, the negative correlations between the levels of Lect-2 and the duration of disease and score for Body mass Index (BMI), CRP and the pain scale have been made. These results not only support the Lect-2 role as a candidate biomarker for OA but also suggest its involvement during the disease evolution and inflammatory processes. Steadying the mechanism of action of Lect-2 such as its involvement in the differentiation of immune cells, response to chemokines, its pharmacological or gene therapies may provide new strategies for the treatment of OA. The value for Lect-2 as a potential OA marker was set for future studies which will involve a much bigger population size for appropriate validation and will make more sense for OA treatment targeting.

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