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ORIGINAL ARTICLE

Is There Any Correlation Between the Systemic Immune Inflammatory Index and Disease Severity in Knee Osteoarthritis?

Diz Osteoartritinde Sistemik İmmün İnflamatuar İndeks Hastalık Şiddeti ile Alakalı mıdır?

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ABSTRACT

Objective: The purpose of this study is to investigate the utility of systemic immune inflammation index as a predictor of disease severity in patients with knee osteoarthritis.
Methods: Two hundred patients diagnosed with knee osteoarthritis according to ACR knee osteoarthritis diagnostic criteria were included in the study. Kellgren-Lawrence staging of knee osteoarthritis, Western Ontario and McMaster University Osteoarthritis (WOMAC) index scores and systemic immune-inflammation index scores were calculated among all participants.
Results: There were 152 (%76) female and 48 (%24) male participants and median score of age was 63 (54,25-70). Fourteen (7%) grade 1 gonarthrosis, 64 (32%) grade 2, 72 (36%) grade 3 and 50 (25%) grade 4 gonarthrosis patients were detected. There was no significant correlation between the systemic immune-inflammation index and the radiological stage of gonarthrosis (Kellgren Lawrens Score) (p=0.238). There was no statistically significant correlation between the systemic immune-inflammation index and WOMAC scores (p=0.593).
Conclusion: The systemic immune-inflammation index did not correlate with disease severity in knee OA.

Keywords: Knee osteoarthritis; inflammation mediators; disease severity; systemic immune-inflammation index

ÖZ

Amaç: Bu çalışmanın amacı diz osteoartiriti olan hastalarda sistemik immün enflamasyon indeksinin hastalık şiddetinin belirleyicisi olarak kullanılabilirliğini araştırmaktır.
Yöntem: ÇalışmayaACR diz osteoarttriti tanı kriterlerine göre gonartroz tanısı almış 200 hasta dahil edildi. Tüm katılımcıların diz osteoartriti Kellgren-Lawrence evrelendirmesi, Western Ontario ve McMaster Üniversitesi Osteoartrit(WOMAC) indeksi skoru ve sistemik immünenflamasyon indeksi belirlendi.
Bulgular: Katılımcıların152'si (%76) kadın 48'si (%24) erkek ve yaşmedyanı 63 (54.25-70) idi. Katılımcılardan 14 (%7) kişide evre 1, 64 (%32) kişide evre 2, 72 kişide (%36) evre 3 ve 50 (%25) kişide evre 4 gonartroz tespit edildi. Sistemik immünenflamasyon indeksi ile gonartroz radyolojik evresi (Kellgren Lawrens Skoru) arasında anlamlı ilişki tespit edilmedi (p=0,238). Sistemik immün-enflamasyon indeksi ile WOMAC skorları arasında istatistiksel anlamlı korelasyon tespit edilmedi (p=0,593).
Sonuç: Sistemik immünenflamasyon indeksinin diz OA'inde hastalık şiddeti ile korele olmadığı tespit edilmiştir.

Anahtar Kelimeler: Diz osteoartriti; Enflamasyon mediatörleri; Hastalık şiddeti; Sistemik immün inflamatuar indeks

Introduction

Osteoarthritis (OA) is the most common form of arthritis. This degenerative and progressive joint disease, which causes disability, loss of function, reduced quality of life and economic burden, affects approximately 250 million people worldwide (1). The prevalence of OA is increasing due to aging of the population and obesity (2,3).

Although OA is considered a degenerative joint disease, it has recently been thought that chronic low-grade synovitis plays a central role in the pathophysiology and adaptive central immunological mechanisms are very important in inflammation and tissue destruction (3,4). In addition, neuroinflammation and central sensitization mechanisms have been shown to play a role in the chronicity of pain in osteoarthritis (5,6). C-terminal telopeptides, cartilage oligomeric matrix protein (COMP), interferon-γ, matrix metalloproteinase-3, adiponectin, interleukins (IL6, IL8, IL10, IL15), and tumor necrosis factor alpha (TNF-a) can be used as biomarkers in knee osteoarthritis (7-9). These are costly and not available at most centers.

The systemic immune-inflammation index (SII) is a new, easily accessible and inexpensive inflammatory biomarker which is calculated by neutrophil, lymphocyte and platelet counts. SII has been shown to correlate with disease activity in a variety of inflammatory-related diseases (10-12).

In this study, the utility of systemic immune inflammation index as a predictor of disease severity was investigated in patients with knee osteoarthritis.

Materials and Methods

A total of 200 patients over the age of 18 diagnosed with gonarthrosis according to the ACR Clinical/Radiographic classification criteria, with

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anteroposterior and lateral knee X-rays taken in the last 6 months, and hemogram results in the last month were included in the study. (13).

Participants were informed about the study and their informed consents was obtained. Exclusion criteria were posttraumatic arthropathy, postinfectious arthropathy, systemic inflammatory disease, systemic infectious disease, active malignancy, and using drugs that may affect platelet, neutrophil and lymphocyte counts.

Radiographic grading of gonarthrosis was evaluated with Kellgren-Lawrence(KL) score and clinical effects were evaluated with Western Ontario and McMaster University Osteoarthritis Index (WOMAC).

The systemic immune inflammatory index was calculated from the hemogram result in the last month using the formula "platelet count x neutrophil count/ lymphocyte count = systemic immune inflammatory index" (14).

The Kellgren-Lawrence score uses four radiographic features: Joint space narrowing, osteophytes, subchondral sclerosis, and subchondral cysts. The severity of radiographic changes increases from grade 0 to 4, and grade 0 means no radiographic features of osteoarthritis, while grade 4 means large osteophytes, significant joint space narrowing, severe sclerosis, and definite bone deformity (13). Classification was performed by an experienced physical therapist.

The WOMAC is a valid and reliable index which is widely used for the evaluation of patients with osteoarthritis. Outcome Measures in Rheumatology Clinical Trials (OMERACT) is a recommended measure for osteoarthritis studies. The WOMAC, validated and reliable in Turkish by Tüzün et al., consists of three sections and 24 questions in which pain, stiffness and physical function are questioned (14). The maximum scores of subgroups are 20 for the pain, 8 for stiffness, and 68 for physical function. High scores indicate increased pain and stiffness and impaired physical function.

Statistics

The analysis of the data was made with IBM SPSS 23.0 (IBM SPSS Statistics, Version 23.0 Armonk, NY: IBM Corp.). Descriptive statistics are given by using the median (1st quartile - 3rd quartile) and % distribution. The normality analysis of the data was analyzed with the Kolmogorov-Smirnov test. Kruskal-Wallis analysis tests were used to compare different groups. Bonferroni correction was applied in the pairwise comparisons of multiple groups. Spearman correlation was used to determine the relationship between variables. A p value under 0.05 was considered statistically significant.

Results

Two hundred people participated in the study with an age median of 63 (54.25-70 years). 152 (76%) of the participants were female and 48 (24%) were male. 14 patients (7%) had grade 1, 64 (32%) had grade 2, 72 (36%) had grade 3 and 50 (25%) had grade 4 gonarthrosis (Table 1).

Relationships between radiological stage, SII value and age is given in Table 2 and Table 3. There was no relationship between the radiological grade of gonarthrosis (Kellgren Lawrens Score) and SII. Median age of the grade 4 patients was higher compared to the other groups (respectively p=0.238, p<0.001).

There was no statistically significant correlation between SII and WOMAC scores. A statistically significant positive correlation was found between age ,WOMAC total and all sub-parameters. The correlations between WOMAC score, SII value and age are given in Table 4.

Table 1: Demographic characteristics of participants

	n=200
Age (year)	63 (54.25-70)
Body Mass Index (BMI) (kg/m²)	27.4 (24-31.2)
Sex (% female)	76

Table 2: Relationship between Kellgren Lawrence Score and SII value and age

Kellgren-LawrenceScore	SII (median (1st quartile - 3rd quartile))	P	Age (median (1st quartile - 3rd quartile))	p
Grade 1	480000 (355000-708000)	0,238	54 (36-65)	<0.001
Grade 2	471500 (379250-670000)		58 (52-66.5)	
Grade 3	411150 (282750-587000)		63.5 (58-70)	
Grade 4	407000 (326000-556760)		67 (64.5-71)	

Kruskal-Wallis test
SII: Systemic immune-inflammation index

Table 3: Relationship between Kellgren Lawrence Score and age

Kellgren- LawrenceScore/Age	Grade 1/ Age	Grade 2/ Age	Grade 3/ Age	Grade 4/ Age
Grade 1/Age	-	0.221	0.017	<0.001
Grade 2/Age	0.221	-	0.01	<0.001
Grade 3/Age	0.017	0.01	-	0.006
Grade 4/Age	<0.001	<0.001	0.006	-

Bonferroni-corrected Mann-Whitney Test. Adjuted p=0.05/6=0.008

Table 4: Relationship between WOMAC score and SII value and age

		WOMAC Pain	WOMAC Stiffness	WOMAC Physical function	WOMAC Total
SII value	**Rho**	-0.062	0.045	-0.056	-.038
p		0.381	0.524	0.429	0.593
n		200	200	200	200
Age	**Rho**	0.199	0.240	0.195	0.205
p		0.001	0.000	0.001	0.000
n		200	200	200	200

Spearman correlation WOMAC: Western Ontario and McMaster University Osteoarthritis Index, SII: Systemic immune-inflammation index

Discussion

The findings of this study showed that a simple ratio (blood SII) from an easily available low-cost test (differential CBC) did not provide information on the radiographic and clinical severity of knee OA. According to our results, no correlation was found between blood SII levels and radiographic and clinical severity of OA in patients with knee OA.

Relationships between the progression of knee osteoarthritis and serum levels of IL-1, IL-10, TNF-, TGF-, keratan sulfate, synovial IL-18, ARGS, and urinary CTX-II have been demonstrated before (17-23). SII is a low-cost biomarker which is calculated by the neutrophil, lymphocyte and platelet counts in the blood and shows systemic inflammation and is available in many laboratories. SII has been shown to have prognostic value in some malignancies and cardiac diseases (24-27). It can also be used to determine the severity of acute pancreatitis and for early detection of sepsis in newborns with congenital heart disease (28,29). SII is an independent risk factor for poor outcome in patients with subarachnoid hemorrhage(30). SII is associated with disease activity in rheumatoid arthritis and ankylosing spondylitis (10,11). There was no relationship between the level of SII and the severity of knee OA in our study. We think that the reason for this is low-grade local inflammation in OA.

The imbalance between catabolic and anabolic activity in the joint that occurs with aging, the poor response of aged chondrocytes to growth factor stimulation and therefore inability to maintain homeostasis in articular cartilage, loss of chondrocytes due to increased susceptibility to apoptosis, meniscus and ligament injuries, and susceptibility to OA due to accumulated inflammatory load are all factors that contribute to OA. Although it can be seen in young people, approximately 50% of individuals over the age of 65 have knee OA(31,32). In our study, age was found as an independent predictor of knee OA, which was consistent with the literature.

The belief that OA is a wear and tear process as a result of mechanical stress has been replaced by the concept that it is a low-grade inflammatory condition in which mechanical stress and immunity acts together. Degraded cartilage fragments by mechanical stress, repeated injuries, and aging produce a sterile inflammatory response (33,34).The long duration of the inflammatory response cause tissue destruction with proinflammatory cytokines and increase in mediators such as proteolytic enzymes and chemokines as well as causes a decrease in anabolic mediators such as anti-inflammatory cytokines and growth factors (33).While proinflammatory cytokines effective in the pathogenesis of OA are IL-1β, TNF-a, IL-6, IL-15, IL-17, IL-18, IL-21, IL-22, anti-inflammatory cytokines are IL-4, IL-10 (36). Besides, chemokines play an important role in inflammation in OA (20). Although some cartilage breakdown products and some of the proinflammatory cytokines are used as biomarkers for OA in scientific studies, their clinical use is currently not possible because they are expensive and not easily accessible. The availability of an easily accessible test to determine the severity of OA may be useful for prognosis prediction and treatment planning in clinical practice.

Limitations

Since the number of participants in this study, which examined a common disease such as OA, was relatively small, it may not be correct to generalize the results. In the study, SII was examined once. A study in which SII was measured at different times or compared with a reliable biomarker could yield more precise results.

Conclusion

In our study, it was determined that SII, an easily accessible and inexpensive inflammatory marker in knee OA, which is a common disease, was not correlated with the severity of the disease. Further studies are reqquired to identify an easily accessible and inexpensive biomarker to be used for prognosis prediction and treatment selection in OA.

Conflict of Interest

None declared by the authors.

Financial Disclosure

None declared by the authors.

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References

1.Bannuru, R.R., et al., Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. Ann Intern Med, 2015. 162(1): p. 46-54.

2.Sacitharan, P.K., Ageing and Osteoarthritis. Subcell Biochem, 2019. 91: p. 123-159.

3.Kulkarni, P., et al., Pathophysiological landscape of osteoarthritis. Adv Clin Chem, 2021. 100: p. 37-90.

4.Geyer, M. and C. Schönfeld, Novel Insights into the Pathogenesis of Osteoarthritis. Curr Rheumatol Rev, 2018. 14(2): p. 98-107.

5.Fusco, M., et al., Degenerative Joint Diseases and Neuroinflammation. Pain Pract, 2017. 17(4): p. 522-532.

6.Geraghty, T., et al., Neuroimmune interactions and osteoarthritis pain: focus on macrophages. Pain reports, 2021. 6(1).

7.Ishijima, M., H. Kaneko, and K. Kaneko, The evolving role of biomarkers for osteoarthritis. Ther Adv Musculoskelet Dis, 2014. 6(4): p. 144-53.

8.Imamura, M., et al., Serum levels of proinflammatory cytokines in painful knee osteoarthritis and sensitization. Int J Inflam, 2015. 2015: p. 329792.

9.Taşoğlu, Ö., et al., Is blood neutrophil-lymphocyte ratio an independent predictor of knee osteoarthritis severity? Clin Rheumatol, 2016. 35(6): p. 1579-83.

10.Satis, S., New Inflammatory Marker Associated with Disease Activity in Rheumatoid Arthritis: The Systemic Immune-Inflammation Index. Curr

Health Sci J, 2021. 47(4): p. 553-557.

11.Wu, J., L. Yan, and K. Chai, Systemic immune-inflammation index is associated with disease activity in patients with ankylosing spondylitis. J Clin Lab Anal, 2021. 35(9): p. e23964.

12.Kim, J.W., et al., Systemic immune-inflammation index combined with ferritin can serve as a reliable assessment score for adult-onset Still's disease. Clin Rheumatol, 2021. 40(2): p. 661-668.

13.Kolasinski, S.L., et al., 2019 American College of Rheumatology/ Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care Res (Hoboken), 2020. 72(2): p. 149-162.

14.Aziz, M.H., et al., The Systemic-immune-inflammation Index Independently Predicts Survival and Recurrence in Resectable Pancreatic Cancer and its Prognostic Value Depends on Bilirubin Levels: A Retrospective Multicenter Cohort Study. Ann Surg, 2019. 270(1): p. 139-146.

15.Kellgren, J.H. and J.S. Lawrence, Radiological assessment of osteo-arthrosis. Ann Rheum Dis, 1957. 16(4): p. 494-502.

16.Tüzün, E.H., et al., Acceptability, reliability, validity and responsiveness of the Turkish version of WOMAC osteoarthritis index. Osteoarthritis Cartilage, 2005. 13(1): p. 28-33.

17.Attur, M., et al., Increased interleukin-1β gene expression in peripheral blood leukocytes is associated with increased pain and predicts risk for progression of symptomatic knee osteoarthritis. Arthritis Rheum, 2011. 63(7): p. 1908-17.

18.Botha-Scheepers, S., et al., Innate production of tumour necrosis factor alpha and interleukin 10 is associated with radiological progression of knee osteoarthritis. Ann Rheum Dis, 2008. 67(8): p. 1165-9.

19.Nelson, A.E., et al., Serum transforming growth factor-beta 1 is not a robust biomarker of incident and progressive radiographic osteoarthritis at the hip and knee: the Johnston County Osteoarthritis Project. Osteoarthritis Cartilage, 2010. 18(6): p. 825-9.

20.Bruyere, O., et al., Biochemical markers of bone and cartilage remodeling in prediction of longterm progression of knee osteoarthritis. J Rheumatol, 2003. 30(5): p. 1043-50.

21.Reijman, M., et al., A new marker for osteoarthritis: cross-sectional and longitudinal approach. Arthritis Rheum, 2004. 50(8): p. 2471-8.

22.Denoble, A.E., et al., Uric acid is a danger signal of increasing risk for osteoarthritis through inflammasome activation. Proc Natl Acad Sci U S A, 2011. 108(5): p. 2088-93.

23.Larsson, S., et al., The association between changes in synovial fluid levels of ARGS-aggrecan fragments, progression of radiographic osteoarthritis and self-reported outcomes: a cohort study. Osteoarthritis Cartilage, 2012. 20(5): p. 388-395.

24.Yuan, M., F. Ren, and D. Gao, The Value of SII in Predicting the Mortality of Patients with Heart Failure. Dis Markers, 2022. 2022: p. 3455372.

25.Huang, H., et al., Prognostic Value of Preoperative Systemic Immune-Inflammation Index in Patients with Cervical Cancer. Sci Rep, 2019. 9(1): p. 3284.

26.Huang, W., et al., The Relationship Between Systemic Immune Inflammatory Index and Prognosis of Patients With Non-Small Cell Lung Cancer: A Meta-Analysis and Systematic Review. Front Surg, 2022. 9: p. 898304.

27.Peng, Y., et al., Positive association between systemic immune-inflammatory index and mortality of cardiogenic shock. Clin Chim Acta, 2020. 511: p. 97-103.

28.Liu, X., et al., Systemic Immune-Inflammation Index (SII) Can Be an Early Indicator for Predicting the Severity of Acute Pancreatitis: A Retrospective Study. Int J Gen Med, 2021. 14: p. 9483-9489.

29.Aydogan, S., et al., Role of systemic immune-inflammatory index in early diagnosis of sepsis in newborns with CHD. Cardiol Young, 2022. 32(11): p. 1826-1832.

30.Zhang, P., et al., Prognostic value of the systemic inflammation response index in patients with aneurismal subarachnoid hemorrhage and a Nomogram model construction. British Journal of Neurosurgery, 2020: p. 1-7.

31.Outerbridge, R.E., The etiology of chondromalacia patellae.J Bone Joint Surg Br, 1961. 43-b: p. 752-7.

32.Coleman, S., et al., A randomised controlled trial of a self-management education program for osteoarthritis of the knee delivered by health care professionals. Arthritis Res Ther, 2012. 14(1): p. R21.

33.Orlowsky, E.W. and V.B. Kraus, The role of innate immunity in osteoarthritis: when our first line of defense goes on the offensive. J Rheumatol, 2015. 42(3): p. 363-71.

34.Berenbaum, F., Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthritis Cartilage, 2013. 21(1): p. 16-21.

35.Molnar, V., et al., Cytokines and Chemokines Involved in Osteoarthritis Pathogenesis. Int J Mol Sci, 2021. 22(17).

36.Scanzello, C.R., Chemokines and inflammation in osteoarthritis: Insights from patients and animal models. J Orthop Res, 2017. 35(4): p. 735-739.