Research Article

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Title: Frequency of asymptomatic hyperuricemia in advanced-stage symptomatic knee osteoarthritis and its relationship with inflammatory parameters.

Short title: Asymptomatic hyperuricemia in advanced-stage symptomatic knee osteoarthritis.

Abstract

Purpose: Hyperuricemia (HU) is thought to be a risk factor in the development and progression of knee osteoarthritis (OA). We sought the frequency of asymptomatic HU in advanced knee OA patients and whether it was related to systemic inflammation.

Materials and methods: This is a single-center, retrospective study including patients with symptomatic stage 3/4 knee OA classified based on Kellgren-Lawrence (K-L) system. Demographic data and serum uric acid (UA), hemogram parameters, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), body mass index (BMI) were recorded. Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and systemic immune-inflammation index (SII)=[(neutrophil count × platelet count)/lymphocyte count] were calculated. Patients with/without hyperuricemia were defined as Group 1 and Group 2, respectively. Demographic and laboratory data were compared between the groups.

Results: Hyperuricemia was present in 51 of 240 patients (21%). There was no significant difference between the groups based on age (Group1: 70.54±7.02, Group2: 68.63±6.29, p=0.07) and BMI (Group 1: 34 kg/m2 (27.7-41), Group2: 32 kg/m2 (25-51.5), p=0.107). NLR, PLR, and SII were similar between two groups (p=0.404, p=0.604, p=0.537). While there was no difference in ESR values between the two groups (p=0.051), CRP levels were found to be significantly higher in Group 1 (p=0.007). A positive correlation was detected between serum UA level and CRP (rho=0.243**, p<0.001), SII (rho=0.173*, p=0.017), NLR (rho=0.154*, p=0.035) and PLR (rho=0.166*, p=0.023) in Group 2. No correlation was detected between serum UA level and ESR, CRP, SII, NLR, PLR and BMI in Group 1.

Conclusion: Asymptomatic HU was found 1 in 5 of advanced-stage knee OA patients and may contribute to inflammation in knee OA. Serum UA level may need to be reduced to normal level in these patients.
Keywords: Asymptomatic hyperuricemia, hyperuricemia, knee osteoarthritis, systemic inflammation

Makale başlığı: İleri evre semptomatik diz osteoartritinde asemptomatik hiperürisemi sıklığı ve inflamatuar parametreler ile ilişkisi.

Kısa başlık: İleri evre semptomatik diz osteoartritinde asemptomatik hiperürisemi.

Öz

Amaç: Hiperüriseminin diz OA gelişmesinde ve ilerlemesinde risk faktörü olduğu düşünülmektedir. Çalışmamızda ileri evre diz OA hastalarında asemptomatik hiperürisemi sıklığı ve sistemik inflamasyonla ilişkili olup olmadığının araştırılması amaçlandı.

Gereç ve yöntem: Semptomatik diz OA olan ve radyografik Kellgren-Lawrence (K-L) sistemine göre derece 3 veya 4 olarak sınıflandırılan hastaları dahil eden tek merkezli, retrospektif bir çalışmadır. Yaş, cinsiyet, komorbiditeler, kullanılan ilaçlar, serum ürik asit (ÜA), hemogram parametreleri, eritrosit sedimantasyon hızı (ESH), C-reaktif protein (CRP) ve vücut kitle indeksi (VKİ) kaydedildi. Nötrofil/lenfosit oranı (NLO), trombosit/lenfosit oranı (TLO) ve sistemik immün-inflamasyon indeksi (Sİİ)=[(nötrofil sayısı × trombosit sayısı)/lenfosit sayısı] hesaplandı. Hiperürisemisi olan ve olmayan hastalar sırasıyla Grup 1 ve Grup 2 olarak tanımlandı ve gruplar arasında demografik ve laboratuvar veriler karşılaştırıldı.

Bulgular: 240 hastanın 51' inde hiperürisemi mevcuttu (%21). Grup 1'de yaş ortalaması 70.54±7.02, BKİ 34 kg/m2 (27.7-41), grup 2' de yaş ortalaması 68.63±6.29, BKİ 32 kg/m2 (25- 51.5), gruplar arasında anlamlı fark yoktu. Grup 1 ve Grup 2 arasında NLO, TLO, Sİİ arasında fark yoktu (p=0.404, p=0.604, p=0.537). Her iki grup arasında ESH değerlerinde fark yokken (p=0.051), CRP düzeyleri grup 1'de anlamlı yüksek saptandı (p=0.007). Grup 2' de ÜA düzeyi ile CRP (rho=0.243**, p<0.001), Sİİ (rho=0.173*, p=0.017), NLO (rho=0.154*, p=0.035) ve PLO (rho=0.166*, p=0.023) pozitif ilişki tespit edildi. Ancak Grup 1' de ÜA düzeyi ile ESH, CRP, Sİİ, NLO, PLO ve VKİ arasında ilişki yoktu.

Sonuç: Çalışmamızda ileri evre diz OA hastalarının yaklaşık 5'de 1'inin asemptomatik hiperürisemisinin olduğu gözlendi. Asemptomatik HÜ, diz OA' da inflamasyona neden olabilir, sonuç olarak bu hastalarda serum ÜA seviyesinin normale çekilmesi gerekebilir.
Anahtar kelimeler: Asemptomatik hiperürisemi, hiperürisemi, diz osteoartriti, sistemik inflamasyon

Introduction

Osteoarthritis (OA) is the most common chronic joint disease worldwide, characterized by cartilage degeneration and subchondral bone damage. The most commonly affected joints are knee, hip, hand and axial joints [1]. In a study conducted in 2020 on the incidence and prevalence of knee osteoarthritis, the global prevalence of knee OA was found 16% and incidence was 203/10,000 person-years [2]. It has begun to be understood that some biochemical factors, as well as mechanical factors, play a role in OA, besides, a subclinical chronic inflammatory process also contributes to the pathogenesis [1].

Uric acid (UA) is the end product of purine metabolism in humans. There may be an increase in serum levels due to the reasons such as lack of excretion or excess production. Different thresholds have been suggested for the definition of hyperuricemia (HU) in different epidemiological studies in the literature [3]. Asymptomatic HU is defined as the presence of serum hyperuricemia in the absence of gout, tophi or urate nephropathy/urolithiasis [4]. HU is the pivotal risk factor in gout and is also suggested to be an important marker in the progression of diseases such as metabolic syndrome, atherosclerotic cardiovascular diseases and ischemic stroke. In the past years, HU was suggested to predict the development of OA in various joints [5]. When serum UA reaches saturation, monosodium urate (MSU) crystals which can accumulate in various tissues such as articular cartilage, synovium, and tendons, begin to form. In vitro studies have shown the anti-oxidant and anti-inflammatory properties of soluble UA [6, 7]. However, MSU crystals formed as a result of the effects of some environmental tissue factors such as low pH and temperature, acquire pro-inflammatory properties. MSU crystals activate NLRP3, an intracellular protein, leading to caspase-1 activation, which causes the formation of the active form of interleukin-1beta (IL-1β) and the production of IL-18, leading to the activation of the innate immune system [8].

In recent years, the relationship between knee OA, the most common type of OA, and hyperuricemia has begun to be investigated due to its frequent association with

metabolic syndrome. Xiao et al. [9], examined the MRI findings of knee OA patients with asymptomatic HU and observed that they were positively associated with synovitis and soft tissue swelling. Another study found a significant relationship between radiographic knee OA and asymptomatic HU, independent of confounding factors such as age, gender and body mass index (BMI) [10].

To determine systemic inflammation, in addition to conventional markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and systemic immune-inflammation index (SII) obtained from hematological parameters are newly used. They have been studied in many fields in recent years as markers of inflammatory response [11-13]. It has been suggested that NLR may be a predictor of the severity of radiographic knee OA [11, 12].

This study sought the frequency of asymptomatic HU in advanced-stage symptomatic knee OA patients and whether HU was associated with systemic inflammation in these patients.

Materials and methods

This is a retrospective study and approval was obtained from the Faculty of Medicine Non-Interventional Clinical Research Ethics Committee. Patients with symptomatic knee OA at least in one knee and classified as stage 3 or 4 according to Kellgren-Lawrence (K-L) radiographic scale [14] indicated with arthroplasty, who admitted to orthopedics outpatient clinic between 1st of January 2021 and 31th of December 2022, were included in the study. Demographic, laboratory and radiological data of the patients were obtained retrospectively.

Exclusion criteria were history of knee injury-trauma or history of knee surgery, diagnosis of inflammatory arthritis (e.g., rheumatoid arthritis, spondyloarthritis, gout or other crystal arthropathy), kidney disease, chronic inflammatory disease, history of cancer. Additionally, patients who used drugs known to cause hyperuricemia (diuretics, aspirin) in the last two weeks were not included in the study. Serum UA, hemogram parameters, ESR, CRP were recorded. NLR, PLR and SII=[(neutrophil count × platelet count)/lymphocyte count] were calculated. Since no standard threshold level is currently used for hyperuricemia; serum UA levels >6.0 mg/dL, which is the level of the risk of developing gout begins to increase, was considered as hyperuricemia [3]. Patients with hyperuricemia were defined as Group 1, normouricemic patients were defined as Group 2, and demographic data and inflammatory markers were compared between these groups.

The Kolmogorov-Smirnov test was used to assess normality of numerical variables. For normally distributed numerical variables, intergroup comparisons were made with independent samples t test, and descriptive statistics were presented as mean and standard deviation (SD). For numerical variables that were not normally distributed, comparison between groups was made with the Mann-Whitney U test and descriptive statistics were presented as median (minimum-maximum). The chi-square test was used for comparison of categorical data. For categorical variables, data were presented as frequencies and percentages. Spearman correlation test was used for correlation analysis and evaluated with rho correlation coefficient, $p<0.05$ was considered statistically significant.

Results

Asymptomatic hyperuricemia (serum UA >6.0) was present in 21.3% of a total of 240 patients (n=51, group 1), and 78.7% (n=189, group 2) was normouricemic. The mean age of the patients was found to be similar (group 1:70.5±7.0 years, group 2:68.6±6.2 years, $p=0.07$). There was no difference between the two groups in terms of body mass index (BMI) (group 1: median 34 [27.7-41] kg/m^2, group 2: median 32 [25-41.5] kg/m^2, $p=0.107$). Gender ratios were female 70% (n=36) and male 30% (n=15) in group 1, female 88% (n=167), male 12% (n=22) in group 2, $p>0.05$. Comorbidity rates were also similar in both groups ($p>0.05$); In group 1, hypertension was 64%, diabetes mellitus was 35%, heart failure was 6%, and renal failure was 2%, while in group 2, hypertension was 59%, diabetes mellitus was 31%, and heart failure was 2%. Demographic characteristics and laboratory data of the groups are delineated in Table-1.

All inflammatory markers (ESR, CRP, SII, NLR, PLR) were found to be higher in Group 1 compared to Group 2, and there was a statistically significant difference in CRP levels. Inflammatory markers of the patients and differences between groups are listed in Table 1.

A positive correlation was detected between serum UA level and CRP, SII, NLR and PLR but no correlation was found between BMI and UA levels in Group 2. No correlation was detected between serum UA level and ESR, CRP, SII, NLR, PLR and BMI in Group 1 (Table 2).

Discussion

Osteoarthritis is the most common chronic joint disease worldwide, and it is understood that it develops not only as a result of mechanical damage, but also as a result of complex pathogenetic mechanisms in which subclinical inflammation occurs

along with some local and systemic biochemical interactions [1, 15, 16]. Considering the frequency of knee OA, the disability it causes, and the economic burden, revealing the risk factors associated with the progression of the disease is very crucial for the management of the disease. The coexistence of knee OA with metabolic syndrome is common. The association between knee OA and several factors such as obesity, dyslipidemia, and impaired glucose tolerance has been investigated [17], and its relation with uric acid has become a matter of ongoing investigation in recent years [9, 10, 18, 19]. Wang et al. [19], examined adults aged 60 years and older with knee OA using the Third National Health and Nutrition Examination Survey (NHANES III) data set and compared patients with asymptomatic HU with normouricemic controls. They found the prevalence of symptomatic knee OA which are K-L stage 2 and above, was significantly higher in the asymptomatic HU group (17.4% and 10.9%, respectively, p=0.04). The NHANES III study reported the frequency of asymptomatic HU as 17.9% in the overall radiographic knee OA (K-L stage ≥2) cohort (n=2213) [19]. In our study, we found the frequency of asymptomatic HU in all knee OA (K-L stages 3 and 4) patients to be similar, at 21%. On the other hand, rates of up to 40% have been reported by other studies [10, 20], but these studies included a small number of patients. Nevertheless, asymptomatic HU was found to have a significantly higher frequency in knee OA patients than in non-knee OA patients, and after controlling potential risk factors associated with knee OA such as age, gender, BMI, education level, occupational activities (e.g., kneeling and squatting) and hypertension, it was observed that asymptomatic HU continued to have a significant association with knee OA (OR=2.61) [10].

In the pathogenesis of OA, especially IL-1β and tumor necrosis factor (TNF) are involved with the degeneration of the articular cartilage matrix [15]. There are different hypotheses about the role of UA in the pathogenesis of knee OA. It is considered that IL-1β and IL-18, which are formed as a result of activation of the NLRP3 inflammasome complex, accelerate bone and cartilage destruction [15, 21, 22]. In a study including 69 knee OA patients, it was found that UA levels in the synovial fluid were strongly correlated with synovial fluid IL-1β and IL-18 levels, thus it was suggested that synovial fluid UA levels were a marker for the severity of knee OA [20]. In our study, despite similar BMI and mean age in the two groups, systemic inflammation markers were detected to be higher in the group with high UA. UA is defined as an endogenous 'danger signal' that stimulates systemic inflammation [23, 24]. Serum UA was found to be strongly correlated with serum CRP, IL-6 and fibrinogen levels in patients with metabolic syndrome, and was also found to be positively correlated with serum TNF-alpha and IL-6 in patients with cardiovascular disease [24]. In our study, inflammation markers were all

higher in the hyperuricemic group, but only CRP reached statistical difference. However, no correlation was observed between serum UA level and ESR, CRP, SII, NLR, PLR in hyperuricemic Group 1. A positive correlation was observed between serum UA level and CRP, SII, NLR, PLR in normouricemic Group 2. These results may be due to the relatively small number of patients in Group 1, moreover, increased levels of inflammatory markers may not always accompany increased levels of serum urate in the patients with asymptomatic hyperuricemia.

The pathogenesis of the relationship between UA and OA is not yet fully elucidated, but increasing evidence suggests that high UA levels may be an important risk factor and/or predictor of disease severity for knee OA [5, 9, 10, 18, 19]. UA may play a role in the development of low-grade inflammatory synovitis in the joint with OA, as well as the increase in IL-1β in the synovial fluid which is thought to be the most responsible cytokine for OA. Studies have determined that the presence of synovitis in knee OA enhances the severity of pain and contributes to the acceleration of joint damage [9, 21].

Our study has some limitations. Since it was thought that subclinical inflammation would be higher in symptomatic patients with advanced-stage OA, the frequency of asymptomatic HU was investigated in these patients, and a comparison was not performed with the patients with early stage knee OA. Due to the retrospective design, clinical measurement tools such as pain scores could not be compared. The level of 6 mg/dl was taken as the hyperuricemia threshold because further imaging methods could not be applied for pre-clinical gout and its effect was tried to be minimized. Obesity may have an effect on serum UA, however, since obesity is common in knee OA patients in our population, the study was not limited to non-obese patients, and the BMI medians were similar between the two groups.

In conclusion, our study showed that one in five patients with advanced-stage knee OA had asymptomatic HU and that asymptomatic HU may be associated with systemic inflammation. It may be plausible to check serum UA levels in advanced-stage knee OA patients scheduled for surgery. The association of serum UA levels with different radiographic stages and pain scores in hyperuricemic patients with knee OA, and whether UA-lowering treatment can help limit OA progression, may be the subjects of new researches.

Conflict of interest: No conflict of interest was declared by the authors.

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Authors' contributions to the article

R.K.C. constructed the main idea and hypothesis of the study. B.B.A. collected the data. V.Y. and F.T.O arranged/edited the material and method section. R.K.C. have done the evaluation of the data in the results section. Discussion section of the article written by R.K.C.and B.B.A. R.K.C reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

Table 1. Characteristics of demographic and laboratory data of the groups

	Group 1 (n=51)	**Group 2 (n=189)**	***p***	**t or z**
Age, mean±standard deviation	70.54±7.02	68.63±6.29	0.07	**3.505**
UA, mg/dl	6.8 (6.1-9.2)	4.4 (2.2-5.9)	**<0.001**	**-10.958**
ESR, mm/h	32.5 (6-77)	24 (1-86)	0.051	**-1.950**
CRP, mg/dl	2.4 (2-30)	2 (2-23)	**0.007**	**-2.680**
SII	1144.2 (142.7-7258.2)	1055.1 (115.4-7842.4)	0.537	**-0.617**
NLR	4.7 (1.5-25)	4.1 (0.7-33.3)	0.404	**-0.834**
PLR	153.9 (66.4-414.2)	147.2 (41.1-621.4)	0.604	**-0.519**
BMI, kg/m^2	34 (27.7-41)	32 (25-51.5)	0.107	**-1.610**

n: number of patients, UA: Uric acid, ESR: Erythrocyte sedimentation rate, CRP: C reactive protein, SII: Systemic immune inflammatory index, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, BMI: Body mass index, Mean ± standard deviation was used for normally distributed data, and median (minimum-maximum) was used for non-normally distributed data. Independent samples t test was used to compare normally distributed data. Mann-Whitney U test was used to compare data that did not show normal distribution. t was the test value of the independent samples, z was the test value of the Mann-Whitney U test
$p<0.05$ was considered statistically significant

Table 2. Correlation between uric acid levels and BMI and inflammatory markers in Group 1 and Group 2

Variables	**Uric acid (mg/dl) in Group 1 (n= 59)**	**Uric acid (mg/dl) in Group 2 (n=181)**
ESH (mm/h)	rho=-0.039, *p*=0.783	rho=0.071, *p*=0.335
CRP (mg/L)	rho=-0.059, *p*=0.679	**rho=0.243**, *p*<0.001**
SII	rho=0.025, *p*=0.861	**rho=0.173*, *p*=0.017**
NLR	rho=-0.048, *p*=0.736	**rho=0.154*, *p*=0.035**
PLR	rho=-0.022, *p*=0.876	**rho=0.166*, *p*=0.023**
BMI, kg/m^2	rho=0.042, *p*=0.770	rho=-0.109, *p*=0.137

n: number of patients, rho: Spearman correlation coefficient, UA: Uric acid
ESR: Erythrocyte sedimentation rate, CRP: C reactive protein
SII: Systemic immune inflammatory index, NLR: Neutrophil lymphocyte ratio
PLR: Platelet lymphocyte ratio, BMI: Body mass index
*The correlation is significant at the level of 0.05
p<0.05 was considered statistically significant

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