The Association of Serum Uric Acid Levels with the Clinical and Radiological Findings in Knee Osteoarthritis: A Cross-Sectional Study

Suchanda Sahu[1]*, Debapriya Bandyopadhyay[2], Sanjukta Naik[3] and Sujit Tripathy[4]

[1]Department of Biochemistry, All India Institute of Medical Sciences (AIIMS), Bhubaneswar, India
[2]Department of Biochemistry AIIMS, Bhubaneswar, India
[3]Department of Biochemistry, Lady Hardinge Medical College, New Delhi, India
[4]Department of Orthopedics, AIIMS Bhubaneswar, India

Corresponding Author*
Suchanda Sahu
Department of Biochemistry, All India Institute of Medical Sciences, India
E-mail: biochem_suchanda@aiimsbhubaneswar.edu.in

Received: 24-Dec-2021, **Manuscript No.** JAHS-22-50537; **Editor assigned:** 26-Dec-2021, **PreQC No.** JAHS-22-50537(PQ); **Reviewed:** 15-Jan-2022, QC No. JAHS-22-50537; **Revised:** 23-Jan-2022(R), Manuscript No. JAHS-22-50537; **Published:** 28-Jan-2022, **DOI:**10.4172/2167-7921.2022.11.058

Abstract

Background: Osteoarthritis (OA), characterized pain and stiffness of joints has many risk factors. Of the many triggers, uric acid has been reported to initiate inflammation and drive the disease to severe forms. However, due to controversial reports, our study was designed to investigate the association of serum Uric Acid (sUA) levels in the different grades of Knee OA.

Methods: This cross-sectional study included 80 patients of knee OA, >40 years of age, of both sexes who had not received any treatment other than analgesics. Subjects were stratified into 4 grades based on Kellgren and Lawrence radiological grading system. A detailed history of signs and symptoms, comorbidities, dietary and drug intake history were taken. The laboratory tests done were erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and sUA. Further reclassification of study population was done as early stage (grades 1 and 2) and advanced stage (grades 3 and 4).

Results: There was no difference in age, ESR and CRP levels in the four grades of OA. However, the sUA was statistically different (p=0.012) in the groups and there was a progressive decrease in the Range of Movement (ROM) with the disease severity (p=0.001). The uric acid levels in males (p=0.044), the ROM (p=0.00038), and the VAS (p= <0.001) were significantly different in the early and advanced stages, but not in females. Uric acid was observed to be negatively correlated (r= -0.235, n=80, p=0.036) with disease severity.

Conclusions: There is an inverse relationship of serum uric acid with knee OA, which may be joint specific. Due to the excess consumption of uric acid in its role as an antioxidant, supplements of antioxidants are suggested. We propose the consideration of subpopulations among knee OA patients whose management should be with the objective of alleviating their discomfort and arresting the disease progression.

Keywords: Hyperuricemia • Hypouricemia • Uric acid • Antioxidant • KL Grades

List of Abbreviations: OA: Osteoarthritis • sUA: Serum Uric Acid • ESR: Erythrocyte Sedimentation Rate • CRP: C-Reactive Protein • ROM: Range of Movement • VAS: Visual Analogue Scale • KL Grades: Kellgren and Lawrence Radiological Grading System

Introduction

Osteoarthritis (OA), also called as 'degenerative arthritis' is characterized pain and stiffness of joints. It affects primarily the large weight bearing joints like hip, spine, knees, hands and feet. The knee joint is the most common site of presentation of OA [1]. It is diagnosed on the basis of clinical examination, radiological findings to grade the OA and laboratory investigations primarily to exclude other forms of arthritis. There are conflicting evidence of the risk factors associated with the progression and severity of knee OA [2]. Studies in the US state that there is a10%-20% clinical presentation, but the prevalence seen as radiological changes can range from 27%-80% [3, 4]. However, the goals of treatment are to alleviate pain so as to keep the elderly patients ambulant and have a good quality of life. The only effective treatment of Knee OA is arthroplasty. This not only burdens the patients financially, but also affects them physically and mentally. Hence it is important to diagnose the OA early and prevent its progress.

Of the many triggers and risk factors studied, it is stated by researchers that uric acid, a normal metabolite of purine catabolism can crystallize in joints and initiate inflammation and progress to severe arthritis [5]. The nosogenesis of OA is continually involved with inflammatory response and the association of hyperuricemia in OA knees have been controversial [5-8]. Hence, we designed this cross-sectional study to investigate the association of the Serum Uric Acid (sUA) levels in the different grades of Knee OA.

Methodology

Study settings

In this cross-sectional study, approved by the Institute Ethical Committee of AIIMS, Bhubaneswar, we recruited eighty patients of both sexes, >40 years of age, who gave written consent to participate. They were diagnosed with OA of knee based on the clinical signs and symptoms like pain, swelling, Range of Movement (ROM) and clinical history from the outpatient department of Orthopaedics. The Norkin and White technique was used to measure the ROM of knees and the maximum was noted for each patient [9]. A Visual Analogue Scale (VAS) was used to measure pain for our patients. It was an 11 point score starting from 0 which was no pain to a maximum of 10 which denoted severe pain which disabled the subject to perform his/her routine activities.

Patients suffering from any kind of infectious disease, autoimmune, acute or chronic inflammatory condition, primary bone malignancy or metastasis were excluded from the study. Patients under treatment with any other drugs or steroids for any other indications or having any h/o alcohol intake or smoking were also excluded from the study. A detailed history of signs and symptoms, comorbidities, dietary and drug intake history were taken and recorded for each subject.

Classification into grades

All the patients were advised weight-bearing Antero-Posterior (AP) and lateral X-ray of bilateral knees. These subjects were stratified into 4 grades based on Kellgren and Lawrence (KL) radiological grading system [10]. The grading (0 through 4) was done as follows:

0-None - No radiographic findings

1-Doubtful- Doubtful narrowing of joint space and possible osteophytic lipping

2- Minimal- Definite osteophytes, definite narrowing of joint space

3-Moderate- Moderate multiple osteophytes, definite narrowing of joints space, some sclerosis and possible deformity of bone contour

4- Severe- Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour

As the above-mentioned categorical observations may or may not be observed in healthy individuals, we did not include a healthy control group in our study.

Sample size

The sample size was calculated keeping the standard normal deviate for β at 0.84 with a power of 80%. Considering a 5% error, our sample size was 80 patients with knee OA.

Biochemical tests

The Erythrocyte Sedimentation Rate (ESR) was measured in whole blood using a modified Westergren method by the automated analyzer Ves-matic Cube 30, Transasia, India. The normal reference ranges were 1 mm/hour-13 mm/hour for males and 1 mm/hour-20 mm/hour for females.

Serum biochemistry included Renal and Liver Function Tests (RFT's; LFT's), uric acid by colorimetric kits and C-Reactive Protein (CRP) by immunoturbidimetric technique. They were measured using AU5800 Beckman Coulter auto-analyser (Beckman Coulter Inc., Brea, CA, USA), using commercially available reagents.

Statistical analysis

Statistical analysis was performed using SPSS 19.0. Data was presented as mean ± Standard deviation as appropriate. The radiological findings were considered as dichotomous data that is either absent/present and were compared using Fisher's Exact test. The comparison between means of the 2 groups early an advanced was done using unpaired student T test. One-way analysis (ANOVA) was done to compare then levels within the 4 grades.

Correlation between variables and disease severity were calculated using Pearson's correlation and $p<0.05$ was considered to be significant.

Results

The general clinical and inflammatory markers compared in Table 1 shows that there was no difference in age, ESR and CRP levels in the four grades of OA. However, the sUA was statistically different (p=0.012) in the groups and there was a progressive decrease in the ROM with the disease severity (p = 0.001) as tested by One-way ANOVA.

Clinical and Biochemical findings in the two groups

The normal reference uric acid levels considered were 155 µmol/L-357 µmol/L for women and 208 µmol/L-428 µmol/L for men. This division further narrowed our groups according to stages. To utilize the statistical tools, we further reclassified our study population as early stage which included grades 1& 2 and advanced stage where grades 3 and 4 were grouped. Table 2 shows that the age, ESR and CRP compared in the two groups were similar. The uric acid levels in males (p=0.044), the ROM (p=0.00038), and the VAS ($p \leq 0.001$) were significantly different in the two stages.

Table 1. General demographic features compared in the different groups.

KL GRADES	1 (n=19)	2(n=22)	3(n=21)	4(n=18)	One-way ANOVA
(SD)Standard Deviat- ion	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	P
Age (years)	52.6 (10.2)	53.0 (9.7)	53.4 (7.2)	56.7 (9.7)	0.509
ESR (mm/hr)	19.6 (12.0)	23.0 (15.9)	23.0 (16.7)	23.5 (18.9)	0.865
Uric Acid (µmol/L)	295.2 (67.5)	323.1 (68.2)	250.1 (72.2)	269.6 (86.4)	0.012
CRP (mg/dl)	1.1(1.3)	2.3 (5.0)	2.8 (4.9)	1.2 (1.1)	0.381
ROM Knees (°)	136.3(6.0)	127.7 (12.3)	122.4 (15.4)	118.3 (16.5)	0.001

Table 2. Comparison general characters in early and advanced stages of OA.

Age (years)	Early	52.8 (9.8)	0.299
	Advanced	55.0 (8.5)	-
ESR (mm/hr)	Early	21.4 (14.2)	0.615
	Advanced	23.2 (17.5)	-
UA (µmol/L) in Females	Early	282.0 (63.5)	0.077
	Advanced	241.7 (72.1)	-
UA (µmol/L) in Males	Early	330.1 (66.0)	0.044
	Advanced	281.7 (83.0)	-
CRP (mg/dl)	Early	1.7 (3.8)	0.686
	Advanced	2.1 (3.7)	-
ROM Knees (°)	Early	131.7 (10.7)	0.00038
	Advanced	120.5 (15.9)	-
VAS score	Early	3.9 (1.3)	<0.001
	Advanced	5.2 (1.2)	-
CHARACTERISTICS	N in Early=41; in Advanced= 39	Mean (SD)	p for TTest

Table 3. Comparison clinical findings in early and advanced stages of OA.

Present in the 2 Stages, as N		Early, N=41		Advanced, N=39		P*
		N	%	N	%	
Comorbidities		7	17.1	12	30.8	0.153
Gait	Normal	34	82.9	19	48.7	<0.001
	Antalgic	7	17.1	17	43.6	
	Varus thrust	0	0.0	3	7.7	
Tenderness		25	61.0	33	84.6	0.019
Swelling		14	34.1	27	69.2	0.002
Effusion		7	17.1	16	41.0	0.019
Deformity	Varus	4	9.8	22	56.4	<0.001
	Valgus	0	0.0	2	5.1	
Analgesic use	None	30	73.2	13	33.3	<0.001
	Intermittent	8	19.5	15	38.5	
	Daily	3	7.3	10	25.6	
Osteophytes		6	14.6	27	69.2	<0.001
Bone defect		2	4.9	19	48.7	<0.001

*Fisher's Exact Test was done to compare the two groups

Table 4. Correlation of Uric Acid with clinical findings.

Correlation with Uric Acid	R	p
Age (years)	0.039	0.73
ESR (mm/hr)	0.199	0.077
CRP (mg/dl)	-0.075	0.511
ROM Knees (°)	0.05	0.659
Comorbidities	-0.094	0.408
Gait	-0.196	0.082
Tenderness	-0.220*	0.05
Swelling	-0.014	0.899
Effusion	0.045	0.695
Deformity	-0.19	0.092
Osteophytes	-0.06	0.595
Bone defect	-0.038	0.739
VAS score	-0.027	0.813
KL grade	-.223*	0.047

*Correlation is significant at the 0.05 level (2-tailed).

The categorical parameters as the presence of clinical findings of OA in Table 3 were represented as frequencies of numbers and percentages. The early and advanced stages compared showed a significant difference in gait ($p \leq 0.001$), tenderness (p=0.019), swelling (p=0.002), effusion (p=0.019), both valgus and varus type of deformity ($p \leq 0.001$), osteophytes ($p \leq 0.001$), and bone defects ($p \leq 0.001$) in the advanced stages of OA. The frequency of use of analgesics was on a daily or intermittent basis in advanced stages as compared to none required by the early stages ($p \leq 0.001$). The presence of comorbidities like hypertension or diabetes or thyroid disorders or more than two diseases were not statistically different in the two stages ($p \leq 0.153$).

Correlation clinical and laboratory findings with sUA

The uric acid levels were found to be decreasing with advancement in disease severity. However uric acid levels were found (Table 4) to be significantly low in advanced stages as compared to early stages (r= -0.318, n=80, p=0.004). Uric acid was observed to be negatively correlated (r= -0.235, n=80, p=0.036) with disease severity. Disease severity was also found to be significantly correlated with the pain scoring Visual Analogue Scale (VAS) (r=0.512, n=80, p<0.001).

Discussion

In this cross-sectional study, which was aimed to find the association

of uric acid with the stages and clinical and radiological findings of knee OA, observed that the sUA levels decreased with an increase in KL grades. The difference in sUA was more prominent in men. Though there are many risk factors associated with disease progression in OA, like age, sex and hormonal status, bone density, genetic factors, nutrition, and other undefined factors, some researchers have attributed hyperuricemia and gout [5, 8, 11-13]. Contrary to these reports we observed that there was a negative correlation of sUA with advanced radiological findings of OA. Similar to our results were reported in a 19-year-old study involving 669 OA patients out of a total of 5842 in the Seventh Korea National Health and Nutrition Examination Survey (KNHANES VII-1) 2016 in the Korean population [7]. They found that the serum uric acid level was significantly higher in subjects without OA than those with OA ($p<0.001$). In the study conducted by Sun et al, they reported that sUA was associated with patients with hip OA but not in knee OA hinting at site-specific pathogenesis. In their review article to study the association of sUA and OA, Ma et al concluded that there is no relationship between the two [14, 15].

As seen in our study, the grades of OA are not correlated with the rise in inflammatory markers, ESR and CRP, suggests that the local inflammation in knee OA is not marked by systemic biochemical estimations. OA, for a long time has been classified as a non-inflammatory disease, involving the entire joint structure. The changes affect the cartilages, synovium, menisci, muscles and ligaments by certain degrees of inflammation which is now documented as being an important part in the pathogenesis and disease progression of OA [16]. The disease progresses at varying rates in individual patients as OA is multifactorial. The initiator of inflammation may or may not be uric acid crystals, it can be due knee injury triggering the recruitment of immune cell and subsequent synthesis of chemokines. The radiological findings give us the lead as to which part of the joint is deranged so as to limit movement of the knee and cause pain. Hence, it is important to subclassify our population of knee OA and target therapy accordingly. Whatever the driving cause for clinical deterioration, the objective of treatment should be to alleviate pain and maintain a decent quality of life. The extent of inflammation can be measured using more specific serological markers rather than ESR or CRP which are more general [16, 17].

In our study we found that there is a statistically significant decrease in sUA levels in men but the decrease was not statistically significant in women. This difference can be explained by the experiment done on adult monkeys and humans which suggest that there are oestrogen receptors on the articular cartilages and that on stimulation by Insulin Like Growth Factors β (ILGF-β) they promote synthesis of proteoglycans and matrix proteins by chondrocytes. Because the hormone status of women and the difference in pathogenesis in both sexes, age and gender should be considered as a variable in management of knee OA patients [18-20].

OA is attributed to oxidative stress and antioxidants help in tissue regeneration and arresting disease progress [21]. The sUA is a part of the Total Antioxidant Capacity (TAC) and there is an increase in sUA with exercise in both knee OA patients and healthy controls suggesting that uric acid which contributes to >50% of the antioxidant effect of plasma will be consumed to form stable complexes in proportion to the amount of free radicals produced [21-23]. As seen in our study, as knee OA progresses (3 and 4 of KL grades) there is an overall decrease in sUA possibly due to increased consumption rather as a cause of disease progression. Henceforth, we can propose that lower serum uric acid levels indicates a need for antioxidants, therefore supplementary vitamins like C and E can be added to the treatment.

The strength of our study was that we had recruited treatment naïve patients or those who had taken only over the counter painkillers for knee OA, hence we have omitted the interference of sUA that would have otherwise been affected by uricosuric drugs and adjuvant therapy. Our limitation was that we did not correct the uric acid levels with body mass index (BMI) and the possibility of purines in diet. However, considering that majority of our population are vegetarians and that there are restrictions on consumption of non-vegetarian diet on certain week days due to local customs, the latter will have minimal interference.

Conclusion

There is an inverse relationship of serum uric acid with knee OA, which may be joint specific. Due to the excess consumption of uric acid in its role as an antioxidant, supplements of antioxidants are suggested. However further clinical trials and cohort studies are required for conclusive evidence. Despite our outcomes, we propose the consideration of subpopulations among knee OA patients whose management should be with the objective of alleviating their discomfort and arresting the disease progression.

Acknowledgements

The authors thank the patients of knee OA who consented to participate and cooperated during the data collection.

Funding

The authors declare that they did not receive any funds for this study.

Reference

1. Cooper, C., et al. "Risk factors for the incidence and progression of radiographic knee osteoarthritis". *Arthritis Rheum* 43. 5 (2000): 995-1000.
2. Bastick, A. N., et al. "What are the prognostic factors for radiographic progression of knee osteoarthritis? a meta-analysis". *Clin Orthop* 473. 9 (2015) :2969-2989.
3. Lawrence, R. C., et al. "Estimates of the prevalence of arthritis and other rheumatic conditions in the United States Part II". *Arthritis Rheum* 58. 1 (2008) :26-35.
4. Kumar, H., et al. "Epidemiology of knee osteoarthritis using kellgren and lawrence scale in indian population". *J Clin Orthop Trauma* 11 (2020):125-129.
5. Ding, X., et al. "The associations of serum uric acid level and hyperuricemia with knee osteoarthritis". *Rheumatol Int* 36. 4 (2016):567-573.
6. Pelletier, J. P., et al. "Osteoarthritis, an inflammatory disease: potential implication for the selection of new therapeutic targets". *Arthritis Rheum* 44. 6 (2001) :1237-1247.
7. Kim S-K, et al. "Serum uric acid level is not associated with osteoarthritis in korean population: data from the seventh korea national health and nutrition examination survey 2016". *Rheumatol Int* 38. 11 (2018) :2077-2085.
8. Krasnokutsky, S., et al. "Serum urate levels predict joint space narrowing in non-gout patients with medial knee osteoarthritis". *Arthritis Rheumatol Hoboken NJ* 69. 6 (2017) :1213-1220.
9. Norkin, C, C, & White, D, J. "Measurement of joint motion: a guide to goniometry". *F A Davis* 5 (2016).
10. Kellgren, J. H, & Lawrence, J. S. "Radiological assessment of osteo-arthrosis". *Ann Rheum Dis* 16. 4 (1957) :494-502.
11. Garstang, S. V, & Stitik, T. P. "Osteoarthritis: epidemiology, risk factors, and pathophysiology". *Am J Phys Med Rehabil* 85 (2006) :02-11.
12. Xiao L, et al. "The association between serum uric acid level and changes of MRI findings in knee osteoarthritis: A retrospective study (A STROBE-compliant article)". *Medicine (Baltimore)* 98. 21 (2019) :15819.
13. Yokose, C., et al. "Gout and osteoarthritis: associations, pathophysiology, and therapeutic implications". *Curr Rheumatol Rep* 18. 10 (2016) :65.
14. Sun, Y., et al. "Serum uric acid and patterns of radiographic osteoarthritis the ulm osteoarthritis study". *Scand J Rheumatol* 29. 6 (2000) :380-6.
15. Ma, C. A, & Leung, Y. Y. "Exploring the link between uric acid and osteoarthritis". *Front Med* 4 (2017) :225.
16. Siebuhr, A. S., et al. "Inflammation (or synovitis)-driven osteoarthritis: an opportunity for personalizing prognosis and treatment?". *Scand J Rheumatol* 45. 2 (2016) :87-98.
17. Egsgaard, L. L., et al. "Identifying specific profiles in patients with different degrees of painful knee osteoarthritis based on serological biochemical and mechanistic pain biomarkers: a diagnostic approach based on cluster analysis". *PAIN* 56. 1 (2011):96-107.
18. Richmond, R. S., et al. "Functional estrogen receptors in adult articular cartilage: estrogen replacement therapy increases chondrocyte synthesis of proteoglycans and insulin-like growth factor binding protein 2". *Arthritis Rheum* 43. 9 (2000) :2081-2090.
19. Loeser, R. F., et al. "The combination of insulin-like growth factor 1 and osteogenic protein 1 promotes increased survival of and matrix synthesis by normal and osteoarthritic human articular chondrocytes". *Arthritis Rheum* 48. 8 (2003) :2188-2196.

20. Kinney, R. C., et al. "Human articular chondrocytes exhibit sexual dimorphism in their responses to 17beta-estradiol". *Osteoarthritis Cartilage* 13. 4 (2005) :330-337.

21. Germanou, E. I., et al. "Oxidative stress and inflammatory responses following an acute bout of isokinetic exercise in obese women with knee osteoarthritis". *The Knee* 20. 6 (2013) :581-590.

22. Wayner, D. D., et al. "The relative contributions of vitamin E, urate, ascorbate and proteins to the total peroxyl radical-trapping antioxidant activity of human blood plasma". *Biochim Biophys Acta* 22. 3 (1987):408-419.

23. Finaud, J., et al. "Oxidative stress: relationship with exercise and training". *Sports Med* 36. 4 (2006) :327-358.

Cite this article: Sahu S, Bandyopadhyay D, Naik S, et al. The Association of Serum Uric Acid Levels with the Clinical and Radiological Findings in Knee Osteoarthritis: A Cross-Sectional Study. J Arthritis, 2022, 11(2), 011-014.