Review Article

The Relationship of Serum Uric Acid with Severity of Knee Osteoarthritis

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Abstract

Background: Knee osteoarthritis (KOA) is a degenerative joint disease with progressive loss of articular cartilage and may lead to disability and individuals with severe KOA may have high serum uric acid (s-UA). This work aimed to assess serum uric acid in individuals with KOA and its relation to disease severity.

Methods: This cross-sectional observational work had been conducted on 150 individuals aged >18 years old, both sexes, with a complaint of knee pain. All patients were subjected to serum uric acid , radiological assessment(plain x ray) and this questionnaire :

The mean Western Ontario and McMaster Universities Arthritis (WOMAC) index

Results: The mean Western Ontario and McMaster Universities Arthritis (WOMAC) index was significantly higher in those with high serum uric acid than patients with normal Serum uric acid (P < 0.001). Kellgren and Lawrence (K-L) grading scale were significantly higher in cases with high serum uric acid than those with normal Serum uric acid. Radiological OA severity indicator (K-L grade) proved to be associated with S. UA such as cases with K-L grade-IV had 3.5 increase in the likelihood of having high Serum uric acid (P= 0.011) compared with those with K-L grade II/III.

Conclusions: Higher Serum uric acid may be associated with higher severity of KOA and radiological findings. In addition, high Serum uric acid concentration may be significantly associated with the duration of the disease

Introduction:

Osteoarthritis (OA) is the predominant degenerative condition, often marked by clinical manifestations such as joint pain and stiffness, and radiological alterations involving joint space narrowing and osteophyte development [1]

OA is significantly correlated with heightened health burden and death rates. The several pathogenic processes involved in the onset and advancement of OA include mechanical stress, inflammatory responses, metabolic abnormalities, and genetic susceptibility; however, the specific contributions of each factor to OA in an individual are not well understood. Physical examinations, radiographies, musculoskeletal ultrasound (MSUS), and recent magnetic resonance imaging (MRI) are employed to diagnose OA and inform treatment [2]

Moreover, several research have explored biochemical markers and biomarkers as non-invasive instruments for diagnosis, forecasting severity of the disease, and assessing therapy response in OA [2]

Uric acid (UA) is a metabolic byproduct of human purine metabolism and is widely acknowledged as a biomarker for many disorders, including cardiovascular disease, metabolic syndrome, and chronic renal failure [3]

There is growing evidence that serum uric acid (s-UA) is pathologically linked to radiographic alterations in OA, including joint space narrowing and osteophyte formation [4]

Moreover, UA in synovial fluid has been proposed to significantly contribute to the development of OA [5]

This work aimed to evaluate Serum uric acid in individuals with knee osteoarthritis (KOA) and its correlation to the disease severity.

Patients and Methods:

This cross-sectional observational work had been conducted on 150 individuals aged >18 years old, both sexes, with a complaint of knee pain. The work had been performed from October 2023 to May 2024 following approval from the Ethics Committee Sohag University Hospitals, Sohag, Egypt (approval code: Soh-Med-23-11-10MS) and registration of clinicaltrials.gov (ID: NCT06149078). An informed

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written consent had been gathered from all participants after explaining the nature of the study. Exclusion criteria were patient with a history of trauma to the knee, and knee complaints as a part of autoimmune connective tissue disease.

Each participant had been exposed to complete taking of history, clinical examinations, rheumatological examination and laboratory investigations [Serum uric acid level] and radiological investigations [plain radiographs.

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) [6]

is a self-administered questionnaire consisting of 24 items divided into 3 subscales:

Pain (5 items): during walking, using stairs, in bed, sitting or lying, and standing upright

Stiffness (2 items): after first waking and later in the day Physical Function (17 items) Plain radiographs of at least one knee [anteroposterior (A/P), lateral} were taken. The knee (A/P) radiographs were graded depending on Kellgren and Lawrence (K/L) grading system (KELLGREN & LAWRENCE, 1957) [7]

Radiographic assessment

Grade: Radiographic findings

Grade 0: No joint space narrowing or osteophyte

Grade 1: Doubtful joint space narrowing, possible osteophytes

Grade 2: Definite osteophytes, possible joint space narrowing

Grade 3: Moderate osteoph:ytes, definite joint space narrowing, some sclerosis, possible bone-end deformity

Grade 4: Large osteophytes, marked joint space narrowing, severe sclerosis, definite bone-end deformity

Statistical analysis

The collected data will be verified, coded by the researcher, and analysed utilising the Statistical Package for Social Sciences (IBM-SPSS/PC/VER 24) *. Descriptive statistics: continuous variables had been displayed as mean ± standard deviation, median, range, and qualitative data was displayed as

frequencies and percentages. Test of significances: Chi square test had been utilised to contrast the difference in distribution of frequencies across different groups. Shapiro-Wilk test will be utilised to test for data normality. Student t-test and Mann-Whitney U test was calculated to test the mean/median differences in continuous parameters between groups (parametric and non-parametric). Multivariate logistic regression analysis will be calculated to measure the significant indicators of ASB (Odds Ratio -OR-, 95% confidence interval -95% CI- and p-value-). Significant test results had been considered when p value was ≤ 0.05.

Results:

The patients' age mean was 52.6 ± 6.9. Also, about two-thirds (68%, n=102) were females and one-third were males (32%, n=48), The mean disease duration was 3.2 ± 2.5 the mean WOMAC score was 48.3 ± 11.1 .The grade of OA disease severity according to K-L system was as follows: 23% grade-II, 47% grade-III and 30% grade-IV .For the serum uric acid level, mean was 6.2 ± 1.5 mg/dl .Moreover, 58% (n = 87) had normal s-UA (< 6.8 mg/dl) and 42% (n = 63) had high s-UA (≥ 6.8 mg/dl). **Table 1**

Table 1: Demographic and clinical data of the studied patients:

		Patients N = 150
Age (years)		**52.63±6.9**
Sex	**Female**	**102(68.0%)**
	Male	**48(32.0%)**
Disease duration (years)		**3.18±0.5**
K-L grading	**G-II**	**34(22.7%)**
	G-III	**71(47.3%)**
	G-IV	**45(30.0%)**
WOMAC		**48.31±11.1**
Serum uric acid level(mg/dl)		**6.15±1.5**
Serum uric acid level category	**normal Serum uric acid level**	**87(58.0%)**
	High Serum uric acid level	**63(42.0%)**

Data are presented as mean ± SD or frequency (%), K-L: Kellgren and Lawrence, G: grade, WOMAC: western Ontario and McMaster universities arthritis index.

The mean disease duration was 3.2 ± 2.5 with a median of 3 years. Also, the mean WOMAC score was 48.3 ± 11.1 with a median of 47. The grade of OA disease severity according to K-L system was as follows: 23% grade-II, 47% grade-III and 30% grade-IV .For the serum uric acid level, it ranged between 3.5 and 8.5 mg/dl with a median of 6.5 and

a mean of 6.2 ± 1.5 mg/dl .Moreover, 58% (n = 87) had normal s-UA (< 6.8 mg/dl) and 42% (n = 63) had high s-UA (≥ 6.8 mg/dl) .

Disease duration and WOMAC index were substantially lower in patients with normal sUA than with elevated sUA (P<0.05). K-L grading was substantially greater in individuals with normal sUA than with elevated sUA (P<0.05) except G-IV was substantially greater in individuals with elevated sUA than patients with normal sUA for the total sample, male and female patients.

Table 2. comparison of different parameters between patients with normal and high serum uric acid

		normal Serum uric acid level (n=87)	High Serum uric acid level (n=63)	P
All patients				
Age (years)		51.87±7.4	53.68±6.2	**0.115***
Sex	**Male**	31(35.6%)	17(27.0%)	**0.262****
	Female	56(64.4%)	46(73.0%)	
Disease duration (years)		2(0.25-15)	3(0.5-10)	**=.001**
WOMAC index		44.07±9.1	54.17±10.9	
K-L grading	**G-II**	34(39.1%)	0(0.0%)	**<0.001***
	G-III	50(57.5%)	21(33.3%)	
	G-IV	3(3.4%)	42(66.7%)	
Male patients				
		normal Serum uric acid level (n=31)	High Serum uric acid level (n=17)	
Age (years)		55.81±5.7	60.41±4.8	**0.007***
Disease duration (years)		1(0.5-4)	3(0.5-10)	**0.002****
WOMAC index		43.29±8.1	45.71±9.4	**0.352***
K-L grading	**G-II**	22(71.0%)	0(0.0%)	**< 0.001****
	G-III	9(29.0%)	10(58.8%)	
	G-IV	0(0.0%)	7(41.2%)	
Female patients				
		normalSerum uric acid level (n=56)	High Serum uric acid level (n=46)	
Age (years)		49.70±7.3	51.20±4.6	**0.232***
Disease duration (years)		3(0.25-15)	4(0.67-10)	**0.190***
WOMAC index		44.50±9.6	57.30±9.8	**<0.001***
K-L grading	**G-II**	12(21.4%)	0(0.0%)	**<0.001****
	G-III	41(73.2%)	11(23.9%)	
	G-IV	3(5.4%)	35(76.1%)	

Data are presented as mean ± SD or frequency (%) or median (IQR). * Significant P value <0.05. *: independent sample t-test, **: Chi-square test, ***: Mann Whitney U test, K-L: Kellgren and Lawrence, G: grade, WOMAC: western Ontario and McMaster universities arthritis index, S: serum, UA: uric acid. Between all patients and females respectively with increase in the WOMAC index, there was increase in the probability of having high Serum uric acid (AOR = 1.054 and1.083, 95% CI 1.004 - 1.106 and1.019 - 1.151) and this was significant (LRT = 0.023 and0.011). This was confirmed by that, cases with K-L grade IV (AOR = 9.468 and13.556, 95% CI 2.332 - 14.325 and6.966 - 41.360) increase in the probability of having high serum uric acid (LRT < 0.001 and< 0.001) compared with those with K-L grade II/III. Between male patients, it was found that with one-year age increase there was increase in the possibility of high Serum uric acid (AOR = 1.196, 95% CI 1.069 – 3.524, LRT = 0.024). Also, with one-year increase in disease duration there was increase in the possibility of high serum uric acid (AOR = 2.443, 95% CI 1.047 – 5.701, LRT = 0.039). Surprisingly, clinical OA severity indicator (WOMAC index) failed to prove to be associated with Serum uric acid (LRT = 0.243). On the contrary, radiological OA severity indicator (K-L grade) proved to be associated with Serum uric acid such as cases with K-L grade-IV had increase in the likelihood of having high serum uric acid compared with those with K-L grade II/III.

Table 3: Multivariable regression for independent association of OA severity and S. UA between all, male and female patients

		Odds Ratio	95% CI*	LRT**P
All patients				
Age (years)		1.071	0.969–1.164	0.180
Sex	**Male**	1.504	0.292–7.758	0.626
Disease duration (years)		1.026	0.768–1.369	0.864
WOMAC		1.054	1.004–1.106	**0.023***
K-L Grade	**Grade-II/III**	1	Ref.	**0.041***
	Grade-IV	9.468	2.332–14.325	**<0.001***
Male patients				
Age (years)		1.197	1.069–3.524	**0.024***
Disease duration (years)		2.443	1.047–5.701	**0.039***
WOMAC		1.014	0.846–1.043	0.243
K-L Grade	**Grade II/III**	1	Ref.	**0.026***
	Grade-IV	3.501	1.102–8.910	**0.011***
Females patients				
Age (years)		1.052	0.909–1.219	0.495
Disease duration (years)		0.972	0.661–1.432	0.888
WOMAC		1.083	1.019–1.151	**0.011***
K-L Grade		--	--	**<0.001***
Grade II/III		1	Ref.	**0.041***
Grade-IV		13.557	6.966–41.340	**<0.001***

*CI= Confidence Interval. * Significant P value <0.05. **LRT: likelihood ratio test, K-L: Kellgren and Lawrence, G: grade, WOMAC: western Ontario and McMaster universities arthritis index

Discussion

KOA is prevalent degenerative joint disease affecting millions worldwide. While the exact pathogenic mechanism of OA remains undetermined, numerous studies indicate that molecules derived from cartilage, synovium, and bone present in synovial fluid, serum, and urine might serve as biomarkers for therapeutic response, diagnosis, and prognostic potential in OA. [2]

UA is the etiological factor of gout associated with hyperuricemia or UA accumulation in synovial fluid [6]

Moreover, several research have demonstrated a correlation between UA and OA [5]

The patients' age with a mean of 52.6 ± 6.9 years. Also, about two-thirds were females and one-third were males. A similar study was conducted on 132 patients of whom 81% were females Gergiev etal [8]

and Angelov et al. Also, van der Eschet al[10], reported female predominance among the included Knee OA patients.

In the current study, 58% had normal sUA (< 6.8 mg/dl) and 42% had high s UA (≥ 6.8 mg/dl).

In the current study, the mean WOMAC index (as indicator for OA severity) was significantly higher in those with high sUA than cases with normal sUA. Additionally, K-L grading showed that cases with high sUA had higher percentage of Grade-IV than those with normal sUA. in our study, Sarker .determined significant positive correlation between sUA and Knee OA severity being higher among grade IV OA [9]

This can be explained as UA might serve as a contributing element in the degenerative progression of OA by initiating the inflammatory cascade. Alternative mechanisms for the correlation between elevated sUA and KOA may encompass genetic predisposition and the endogenous hormonal milieu. Additionally, a plausible explanation is that increased UA levels could facilitate the formation of microcrystals within the joint space, instigating an

inflammatory cascade that contributes to OA. Howard et al[4].

found a relationship of sUA and OA severity which significantly more among patients with high UA level. In contrary, Bassiouni et al[10]

revealed no significant association between sUA level and duration of Knee OA

Cases with high sUA were significantly older than those with normal sUA. Also, the disease duration was significantly shorter among cases with normal sUA compared with those with high sUA. It was found that with one-year age increase there was 20% increase in the possibility of high Serum uric acid. Also, with one-year increase in disease duration there was 2.4 times increase in the possibility of high sUA.

The current work revealed the multivariable regression analysis of the independent relationship between sUA and OA disease severity either clinical or radiological among females. After adjusting for age and disease duration, both clinical/radiological OA severity indicators prove to be correlated with sUA. A study conducted on 200 Knee OA patients to explore the correlation of sUA level with clinical and radiological severity. The multi-regression analysis revealed a substantial association between KOA severity and sUA level. In line with Ding et al [11]

study which was conducted on 4685 subjects to examine association of sUA and radiographic features of OA. It revealed that KOA was significantly associated with high uric acid level especially in females. Similarly, Denoble et al [12]

reported that sUA level was significantly correlated with OA severity in non-gouty patients. Xiao et al[13]

concluded that Knee OA patients with elevated sUA were more prone to possess severe MRI findings. A study was conducted by Xiao et al[13].

showed that individuals with higher sUA had substantially more severe WOMAC score of the three subscales: pain, stiffness, and function in addition to total WOMAC score. In contrary, Bajwa et al[13,14]

conducted a study on 100 Knee OA patients to identify link between increased uric acid and OA

and revealed no significant relation between increased UA and severity of Knee OA.

Limitations of the work involved that the sample size was relatively small. So, we recommended that Serum uric acid may be useful marker for determination of severity of Knee OA. Duration of Knee OA may be an independent factor for hyperuricemia and disease severity so we recommend that serum uric acid may be useful marker for determination of severity of

knee osteoarthritis, duration of knee osteoarthritis may be an independent factor for, hyperuricemia and disease severity, further longitudinal studies with large sample size may be needed for further estimation of uric acid and relation to severity of knee osteoarthritis

Conclusions:

Higher Serum uric acid is associated with higher severity of Knee OA and radiological findings. In addition, duration of the disease significantly had high uric acid concentration. In addition, the mean WOMAC index (as indicator for OA severity) was significantly higher in those with high Serum uric acid group than cases with normal Serum uric acid group. Additionally, K-L grading revealed that cases with high serum uric acid had higher percentage of Grade-IV than those with normal Serum uric acid. In the multivariable regression analysis of the independent correlation between Serum uric acid and OA disease severity either clinical or radiological, after adjusting for age and sex and disease duration, both clinical and radiological OA severity indicators proved to be associated with Serum uric acid.

Recommendations:

Multicenter studies and longitudal follow up by plain x ray and serum uric acid.

Further longitudinal studies with large sample size may be needed for

further estimation of uric acid and relation to severity of knee osteoarthritis

Approval and ethical number: Soh-Med-23-11-10MS

References:

1. Loeser RF, Pathmasiri W, Sumner SJ, McRitchie S, Beavers D, Saxena P, et al. Association of urinary metabolites with radiographic progression of knee osteoarthritis in overweight and obese adults: an exploratory study. Osteoarthritis Cartilage. 2016;24(8):1479-86.

2. Hao HQ, Zhang JF, He QQ, Wang Z. Cartilage oligomeric matrix protein, C-terminal cross-linking telopeptide of type II collagen, and matrix metalloproteinase-3 as biomarkers for knee and hip osteoarthritis (OA) diagnosis: a systematic review and meta-analysis. Osteoarthritis Cartilage. 2019;27(5):726-36.

3. Bardin T, Richette P. Impact of comorbidities on gout and hyperuricaemia: an update on prevalence and treatment options. BMC Med. 2017;15(1):123.

4. Howard RG, Samuels J, Gyftopoulos S, Krasnokutsky S, Leung J, Swearingen CJ, et al. Presence of gout is associated with increased prevalence and severity of knee osteoarthritis among older men: results of a pilot study. J Clin Rheumatol. 2015;21(2):63-71.

5. Vaidya B, Bhochhibhoya M, Nakarmi S. Synovial fluid uric acid level aids diagnosis of gout. Biomed Rep. 2018;9(1):60-4.

6. Bellamy, N., Buchanan, W. W., Goldsmith, C. H., Campbell, J., & Stitt, L. W. (1988). Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. The Journal of Rheumatology, 15(12), 1833–1840.

7. KELLGREN, J. H., & LAWRENCE, J. S. (1957). Radiological Assessment of Osteo-Arthrosis. Annals of the Rheumatic Diseases, 16(4), 494–502. https://doi.org/10.1136/ARD.16.4.494

8. Chhana A, Callon KE, Pool B, Naot D, Gamble GD, Dray M, et al. The effects of monosodium urate monohydrate crystals on chondrocyte viability and function: implications for development of cartilage damage in gout. J Rheumatol. 2013;40(12):2067-74.

9. Georgiev T, Angelov AK. Modifiable risk factors in knee osteoarthritis: treatment implications. Rheumatol Int. 2019;39(7):1145-57.

10. van der Esch M, Knoop J, van der Leeden M, Roorda LD, Lems WF, Knol DL, et al. Clinical phenotypes in patients with knee osteoarthritis: a study in the Amsterdam osteoarthritis cohort. Osteoarthritis Cartilage. 2015;23(4):544-9.

11. Sarker S, Kamal T, Dina N, Sharmin S. Association of serum uric acid with the severity of knee osteoarthritis in a tertiary care hospital. Orthop J Sports Med. 2023;5(2):41-6.

12. Bassiouni SARAK, El Adalany MA, Abdelsalam M, Gharbia OM. Association of serum uric acid with clinical and radiological severity of knee osteoarthritis in non-gouty patients. ERAR. 2021;48(12):1-10.

13. Ding X, Zeng C, Wei J, Li H, Yang T, Zhang Y, et al. The associations of serum uric acid level and hyperuricemia with knee osteoarthritis. Rheumatol Int. 2016;36(4):567-73.

14. Denoble AE, Huffman KM, Stabler TV, Kelly SJ, Hershfield MS, McDaniel GE, 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):2088-93.

15. Xiao L, Lin S, Zhan F. The association between serum uric acid level and changes of MRI findings in knee osteoarthritis: A retrospective study (A STROBE-compliant article). Medicine (Baltimore). 2019;98(21):e15819.

16. Bajwa RS, Gautam R, Pathak SK, Sharma A, Pruthi V, Verma V. Study of correlation of hyperuricemia with knee osteoarthritis. Indian J Public Health Res Dev. 2020;11(2).