

## Association of Serum Uric Acid Level and Knee Osteoarthritis: A cross-sectional study.

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### Abstract

**Background:** Serum uric acid (SUA) level is an important biomarker for metabolic diseases and it is related to many forms of arthritis including OA. Many studies have been published showing direct association of elevated serum uric acid level (hyperuricemia) and progression of radiographic changes in OA. However, few studies have shown no significant association. In such controversy, a cross sectional study is designed to evaluate the association between serum uric acid level and radiographic OA of the knee.

**Methods:** Adult patients (Age >18 years) with the complaint of knee pain without any history of recent or old trauma were included in the study. Following patients were excluded: non-OA joint disease; known cases of hyperuricemia; patients with generalized OA and missing data. The SUA concentration was classified into 4 quartiles: <4.5, 4.5 to <5.5, 5.5 to 6.5 and >6.5 mg/dl. The plain radiographs of the affected knee were examined using the Kellgren–Lawrence (K–L) radiographic atlas. Differences in continuous data were evaluated by the one-way classification ANOVA whereas differences in category data were assessed by the Chi-square test. Odds ratios (ORs) with 95% confidence intervals (CIs) for the association between radiographic knee OA and serum uric acid level were calculated for each concentration quartile (reference <4.5mg/dl). All data recording and analysis were done using SPSS version 22.0.

**Results:** A total of 246 (n) underwent final analysis, 105 were men and 141 were women with mean (SD) age 60.4 (10.5) years (range, 40 to 78 years) and 52.2 (11.4) years (range, 36 to 84 years) respectively. Hyperuricemia (SUA>6.5mg/dl) was observed among 85 (34.6%) patients and the prevalence of radiographic OA of the knee was 95.2%. The difference was significant (P<0.05) across all quartiles of SUA for the prevalence of OA knee. Odds ratio {ORs (95% CI)} for radiographic OA of the knee among patients with 4<sup>th</sup> quartile of SUA (i.e. >6.5mg/dl) was 6.61 (2.0 to 20.9) and adjusted ORs (95% CI) with age, sex and BMI was 6.4 (1.7 to 23.2). P for trend was <0.05.

**Conclusion:** There is a direct association of elevated SUA level and radiographic OA of the knee. Hence, routine SUA level testing in patients with radiographic OA of the knee is helpful for timely management and prevention of disease progression. However, studies with larger sample size are essential to justify this recommendation.

**Keywords:** hyperuricemia; arthritis; K-L grading; Odds ratio

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### I. Introduction

Uric acid is the by product of purine metabolism and found largely as urate (ion form) in the body fluid.<sup>1</sup>Uric acid concentration in the blood depends upon urate synthesis and excretion.<sup>1</sup>Hyperuricemia is defined as an elevated SUA level more than the upper limit of the normal range. The widely accepted upper end of normal range of SUA is 6 mg/dl in women and 6.8 mg/dl in men.<sup>2</sup>Hyperuricemia is an important biomarker for metabolic diseases and is also related to many forms of arthritis including osteoarthritis.<sup>3</sup>

Osteoarthritis (OA) is characterised by synovitis, degradation of articular cartilage and subchondral sclerosis.<sup>4</sup> It is a major public health issue and a leading cause of disability. It is believed that, the occurrence and progression of OA depends on multiple factors, including aging, mechanical stress and metabolic factors.<sup>5</sup> Out of these factors, the association of metabolic factors is poorly understood. It is believed that there is

pathological link between hyperuricemia and OA. Several authors<sup>5-12</sup> advocated a significant association between hyperuricemia and progression of OA. However, few authors<sup>13-15</sup> found no significant association.

A study conducted by Cheryl Ann Ma and Ying Ying Leung<sup>16</sup> reviewed 66 papers from the literature and tried to identify a link between SUA and OA. They concluded that both the gout and OA may have same pathogenesis and OA can be managed with anti-gout medications. However, they could not find conclusive evidence to support the idea of a causal association between SUA and OA. Hence, they advised for further study to evaluate the link between SUA and OA.

Therefore, we conducted a cross-sectional study to evaluate an association between elevated SUA and radiographic OA of the knee.

## Patients and Methods

### Study Population

This cross-sectional study was carried out in the out-patient clinic of department of orthopedics at Universal College of Medical Sciences, Bhairahawa, Nepal. The duration of study was 6 months (from February 2019 to August 2019). Adult patients (Age >18 years) with the complaint of knee pain without any history of recent or old trauma were included in the study. All included patients provided written informed consent. Basic characteristics, such as age, sex, occupation, duration of illness, and BMI (in kg/m<sup>2</sup>) were recorded. Plain antero-posterior and lateral view radiographs of the affected knee were taken and serum uric acid level (in mg/dl) was obtained. Then, following patients were excluded: non-OA joint disease; known cases of hyperuricemia; patients with generalized OA and missing data.

### Blood Biochemistry and Assessment of Radiographic OA of the Knee

SUA Level testing was performed by spectrophotometry method using *Humaster 600*. The SUA concentration was classified into 4 quartiles: <4.5, 4.5 to <5.5, 5.5 to 6.5 and >6.5 mg/dl. The plain radiographs of the affected knee were examined by two independent orthopedic surgeons using the Kellgren–Lawrence (K–L) radiographic atlas<sup>17</sup>. Disagreements between the 2 surgeons, if any, were resolved through discussion. OA of the knee was classified into 5 categories based on K–L grade: 0 = absence of OA; 1 = suspected OA; 2 minimal OA; 3 = moderate OA; 4 = severe joint OA. Diagnosis of radiographic OA of the knee was confirmed, if at least 1 knee joint was rated as K-L grade 2 or higher.

### Statistical Analysis

Continuous data were expressed as the mean (SD) and category data were expressed as proportion (%). Differences in continuous data were evaluated by the one-way classification ANOVA whereas differences in category data were assessed by the Chi-square test. Odds ratios (ORs) with 95% confidence intervals (CIs) for the association between radiographic knee OA and serum uric acid level were calculated for each concentration quartile. First quartile (i.e. SUA < 4.5 mg/dl) was set as a reference category. Adjusted ORs with age, sex and BMI were calculated using binary logistic regression model. *P* for trend is calculated using Chi-square test and level of significance was set on 0.05. Correlation was analyzed using correlation coefficient and test of significance was done using two-tailed t-Test. All data recording and analysis were done using SPSS version 22.0.<sup>18</sup>

## II. Literature review

We searched pubmed [MEDLINE] database using keywords, such as, “serum uric acid”, “hyperuricemia”, “metabolic syndrome” and “osteoarthritis”. The relevant article was selected after reviewing title, abstracts and full-texts.

## III. Results

Out of 505 patients who were selected initially, only 246 (n) underwent final analysis following pre-determined exclusion criteria. Among 246 patients, 105 were men and 141 were women. Mean (SD) age of the patients was 60.4 (10.5) years (range, 40 to 78 years) and 52.2 (11.4) years (range, 36 to 84 years) among men and women respectively.

Hyperuricemia (SUA >6.5mg/dl) was observed among 85 (34.6%) patients. The basic characteristics of patients according to the quartiles of serum uric acid concentration were shown in table 1. [Table 1]

**TABLE 1. Basic characteristics among 246 patients according to quartiles of SUA concentration**

Characteristics	Quartiles of serum uric acid				P value
	Q1(lowest)	Q2	Q3	Q4(highest)	
Participants (n)	65 (26.4)	52 (21.1)	44 (17.9)	85 (34.6)	-
Median Uric acid level (mg/dl)	4.0	4.9	6.0	7.7	-
Age (years)	49.7 (11.5)	58.7 (11.8)	54.0 (9.0)	59.3 (11.3)	<b>0.00*</b>

<b>BMI (kg/m<sup>2</sup>)</b>	25.0 (2.1)	26.7 (2.1)	26.3 (2.3)	26.9 (2.2)	<b>0.00*</b>
<b>Female %</b>	76.9	76.9	47.7	35.2	<b>0.00#</b>
<b>Duration of illness (months)</b>	24.4 (18.3)	22.5 (14.2)	22.0 (16.4)	20.9 (13.9)	<b>0.59*</b>
<b>Occupation</b>					
Household/non-worker	5 (10.0)	10 (20.0)	5 (10.0)	30 (60.0)	
Farmer	30 (34.9)	15 (17.4)	11 (12.8)	30 (34.9)	<b>0.00#</b>
Service	15 (37.5)	2 (5.0)	13 (32.5)	10 (25.0)	
Business/trade	15 (21.4)	25 (35.7)	15 (21.4)	15 (21.4)	

Data are expressed in mean (SD) and percentage

\*Test of significance done across all quartiles of serum uric acid level using one way ANOVA, level of significance 0.05

#Test of significance done across all quartiles of serum uric acid level using Chi-square test, level of significance 0.05

The prevalence of knee OA was 86% (n=246) and 95.2% (n=85) among all patients and patients with SUA>6.5mg/dl, respectively. The distribution of involved knee, knee OA and K-L grading based on quartiles of SUA was shown in table 2. [Table 2]

**TABLE 2. Assessment of involved knee among 246 patients and association with quartiles of serum uric acid concentration**

Characteristics	Quartiles of serum uric acid concentration				P value
	Q1(lowest)	Q2	Q3	Q4(highest)	
<b>Knee involved</b>					
Left	25 (38.5)	10 (15.4)	6 (9.2)	24 (36.9)	
Right	20 (18.9)	27 (25.5)	38 (35.8)	21 (19.8)	<b>0.000#</b>
Both	20 (26.70)	15 (20.0)	0 (0.0)	40 (53.3)	
<b>Knee OA</b>	49 (22.9)	43 (20.1)	41 (19.2)	81 (37.9)	<b>0.002#</b>
<b>K-L grade</b>					
Grade 1	16 (50.0)	9 (28.1)	3 (9.5)	4 (12.4)	
Grade 2	39 (40.2)	16 (16.5)	18 (18.6)	24 (24.7)	<b>0.000*</b>
Grade 3	10 (10.9)	22 (23.9)	18 (19.6)	42 (45.7)	
Grade 4	0 (0.0)	5 (20.0)	5 (20.0)	15(60.0)	

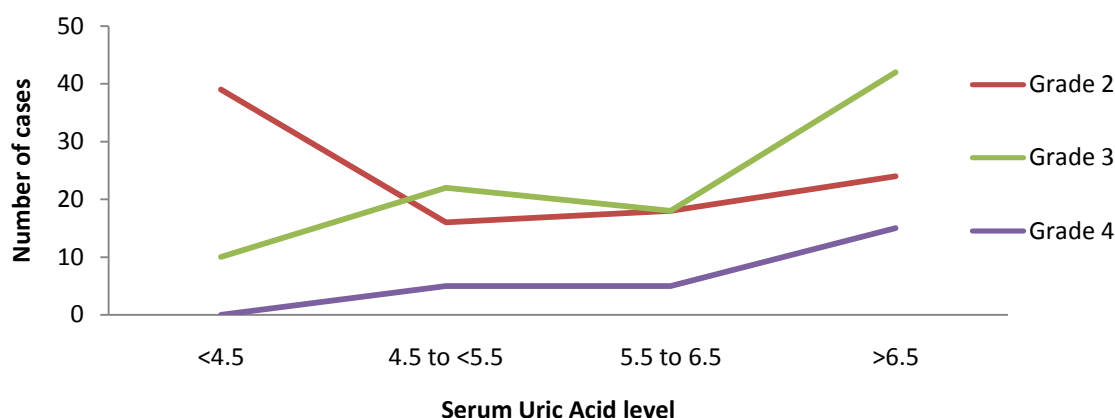
Data are expressed in number and percentage

#Test of significance done across all quartiles of serum uric acid level using Chi-square test, level of significance 0.05

\*Test of significance done across all quartiles of serum uric acid level using Chi-square test, level of significance 0.05 with one cell having expected count less than 5

Among patients with SUA>6.5 mg/dl (n=85), 28.2% had mild, 49.4% had moderate and 17.6% had severe radiographic OA of the knee (K-L grading). The correlation of SUA level and radiographic OA of the knee (K-L grading) was shown in figure 1. [Figure 1]

**Figure 1. Correlation# between SUA level and Radiographic OA of the knee**



#Correlation is significant at 0.05 level (P = 0.00)

Odds ratio {ORs (95% CI)} for radiographic OA of the knee among patients with 4<sup>th</sup> quartile of SUA (i.e. >6.5mg/dl) was 6.61 (2.0 to 20.9) and adjusted ORs (95% CI) with age, sex and BMI was 6.4 (1.7 to 23.2). The association of SUA level and radiographic OA of the knee were shown in table 3. [Table 3]

**TABLE 3. Association of serum uric acid and radiographic knee OA among 246 patients**

Characteristics	Serum uric acid quartiles				P for trend
	Q1(lowest)	Q2	Q3	Q4(highest)	
Median uric acid concentration (mg/dl)	4.0	4.9	6.0	7.7	
Participants (n)	65	52	44	85	
Knee OA (n)	49	43	41	81	
ORs (95% CI)	1.00 (reference)	1.56 (0.6 – 3.8)	4.46 (1.2 – 16.3)	6.61* (2.0 – 20.9)	<b>0.001#</b>
Age, Sex, BMI adjusted ORs (95% CI)	1.00 (reference)	1.26 (0.4 – 3.4)	4.97 (1.2 – 20.0)	6.4* (1.7 – 23.2)	<b>0.000#</b>

Odds ratio (95% CI) are adjusted setting lowest concentration < 4.5mg/dl as reference value, \* P value < 0.05 relative to low SUA level (i.e. <4.5 mg/dl).

#### IV. Discussion

In our study, hyperuricemia was prevalent among men with advancing age. The average age of the patients with SUA >6.5 mg/dl was 59.3 years and 64.8% were men. These outcomes were similar to that reported in previous studies<sup>6,7</sup>. Sun et al.<sup>6</sup> also Suggested that the SUA level increases with increase in age. Our results also showed similar outcomes and the difference across all quartiles was statistically significant. However, there was variation in average values which is due to the unequal sample size in each quartiles.

The prevalence of radiographic OA increases with increase in SUA level. In this study, the prevalence of radiographic OA of the knee was higher (95.2%) among patients with hyperuricemia (SUA level >6.5 mg/dl). A significant difference (p<0.05) was observed across all quartiles of SUA. This outcome is similar to that of Jitsu et al.<sup>10</sup>. Jitsu et al.<sup>10</sup> conducted a similar kind of cross sectional study with 830 patients and found high prevalence of isolated knee OA among patients with hyperuricemia.

K-L grading system for the evaluation of radiographic OA is a widely accepted grading system<sup>17, 19</sup>. In this study, there was a strong correlation between serum uric acid level and radiographic OA for grade 2 and grade 4 OA changes. A slight fluctuation in a graph was seen for grade 3 OA changes. This is due to the uneven number of participants and close window of SUA level.

Several studies<sup>8-10, 20</sup> have shown positive association of hyperuricemia and radiographic OA changes. Schouten et al.<sup>8</sup> in their cohort of 142 patients found significant association between highest tertile of SUA and radiographic OA knee. Similarly, Krasnokutsky et al.<sup>9</sup> in their cohort of 88 patients identified elevated SUA level is associated with joint space narrowing in the weight bearing area of the knee. In our study, we also identified that there was up to 7-times higher chance (Odds 6.61) of having radiographic OA knee among patients with hyperuricemia compared to the lowest reference value and the association of elevated SUA and radiographic knee OA was statistically significant.

Felson et al.<sup>13</sup> in their cohort of 1420 patients found no significant association of SUA and knee and generalized OA after adjusting for age, sex and BMI. Similarly, Hart et al.<sup>14</sup> in their case control study involving 118 cases over 861 controls observed no association of SUA and OA knee after adjusting for age and BMI. In addition, similar outcome was reported by Baggie et al.<sup>15</sup> and Ding et al.<sup>7</sup> However, our results showed significant association of elevated SUA and radiographic OA of the knee even after adjusting with age, sex and BMI. Our reports are similar to that reported by Jitsu et al.<sup>9</sup>, Al-Afraz et al.<sup>10</sup>, and Howard et al.<sup>11</sup>. They have also reported higher Odds when adjusted to age, sex and BMI and the difference was statistically significant.

The strengths of our study are: a well conducted cross-sectional study; all patients provided informed consent; no loss of data; a detailed statistical analysis; and review of available literature. However, our study also has some limitations: small sample size; unequal number of participation in study groups; only patients with hyperuricemia were taken into account during most statistical analysis; other potential covarites like HTN, DM, smoking and level of activities were not included in the study; and there is intra-observer variability in obtaining K-L grading, so our study may have investigator bias.

#### V. Conclusion

According to our observations, we conclude that there is a pathological link between hyperuricemia and osteoarthritis. There is a direct association of increase in SUA level and progression of radiographic OA changes. Hence, a routine testing of SUA level in patients with suspected OA is recommended. However, a similar study with large sample size and including several confounding covariates is required to further justify the recommendation.

**Conflict of interest: N/A**

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