

## ORIGINAL RESEARCH

# The Association of Serum Calcium and Serum Uric Acid Level with Knee Osteoarthritis- A Cross Sectional Study

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### ABSTRACT

**Background:** Many studies have described a relationship among serum calcium and uric acid level with osteoarthritis in recent past, but studies on evidence of relationship among serum uric acid and knee joint osteoarthritis are limited. Present study is intended to validate the association between serum calcium and uric acid levels with osteoarthritis of knee joint.

**Methods:** This is a cross sectional observational study including 340 patients with clinically diagnosed osteoarthritis of knee. Patient's radiographs of affected knees and hands were obtained along with their serum calcium and uric acid level, Rheumatoid factor and C reactive protein level. Keligren-Lawrence osteoarthritis scale was used for grading of knee osteoarthritis roentgen graphically. On the basis of serum uric acid levels, all the patients were divided in to three groups according to serum uric acid level Group 1: - serum uric acid less than 5mg/dl, Group 2: - serum uric acid levels between 5.1-7 mg/dl, Group 3: - serum uric acid levels greater than 7 mg/dl.

**Results:** Out of 340 patients, 238 patients (70 %) diagnosed as isolated knee joint osteoarthritis, generalized osteoarthritis is seen in 66 (19.6%) Patients, and Rheumatoid Factor, along with C-reactive protein is positive in 36(10.5%) patients. Association of osteoarthritis of knee joint, generalized osteoarthritis with the highest tertile of serum uric acid level found to be strongly positive [adjusted odds ratio- 2.31 and adjusted odds ratio- 3.27 respectively]. Also association between increasing serum uric acid levels and progression of the osteoarthritis of knee found to be positive.

**Conclusion:** This study supports a possible correlation between hyperuricemia and knee joint osteoarthritis. Hypercalcemia were inversely associated to the knee osteoarthritis.

**Key words:** Knee Osteoarthritis; Serum uric acid. Serum uric acid, hyperuricemia

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### Introduction

Osteoarthritis is the commonest type of arthritis in orthopedics practice, leading cause of chronic pain, impaired mobility, and reduced quality of life in the elderly population [1]. The association of osteoarthritis with age, obesity, sex, and metabolic factors has already been established by studies in past [2-7]. Many of these studies showed significant association between osteoarthritis and obesity. Some of the studies on serum uric acid, showed no association between it and osteoarthritis [3-5]. Some study found a positive association between knee osteoarthritis and uric acid but association was insignificant [2]. Recently, Kono et al [8]

demonstrated that uric acid regulates the inflammation induced by tissue injury, in mouse model. These data form the basis for our hypothesis that presence of uric acid in synovial fluid determines tissue inflammation, disease severity, and progression in osteoarthritis (OA). Robinson et al [9] in their study demonstrated a positive association of serum uric acid level with osteoarthritis of multiple joints. Roddy E, Zhang W et al [10] in their study noted the apparent co-localization of gout attacks and radiographic OA at multiple joints (big toe, ankle, knee, and distal finger joints) and suggested that OA may be developed by the localized deposition of monosodium urate crystals.

Calcium has a role in digestion and regulating blood pressure [3] and makes an important contribution to maintaining bone homeostasis, as well as in bone remodeling. The bone consists of an organic component containing mainly type I collagen with a role in flexibility and an inorganic component with a role in ensuring resistance to compressive forces, consisting mainly of Ca and other mineral [12]. There is an increasing prevalence of different kinds of arthritis and hyperuricemia worldwide due to increasing use to high caloric diet, higher prevalence of obesity, use of medications like diuretics and intake of fructose in various kinds of beverages [11].

Present study was done to find the association between serum calcium and serum uric acid level with knee osteoarthritis patients.

### Materials & Methods

This study was a cross sectional observational study, carried out in the collaboration of department of biochemistry and orthopedics in a tertiary care center at central India. A total of 340 patients of knee osteoarthritis were enrolled in this study. These patients with complaints of various joints pain attended the department of Orthopaedics from March 2020 to March 2021. Patients included in study, were with age more than forty-five years, persistent knee pain more than one month which is insidious in onset and having crepitus during movement of knee joint and roentgen graphic evidence of osteoarthritis. In this study patients suffering from knee osteoarthritis of grade 2 or more (according to Kellgren-Lawrence osteoarthritis scale) are included [13]. This system has the following grading of knee osteoarthritis:

Grade 0: no radiographic features of OA

- Grade 1: doubtful joint space narrowing and osteophyte
- Grade 2: possible Joint space narrowing definite osteophyte
- Grade 3: definite Joint space narrowing, multiple osteophyte possible bony deformity and mild sclerosis

- Grade 4: obliterated joint space, large osteophyte, definite bony deformity and severe sclerosis

Generalized osteoarthritis was defined as presence of radiographic changes of osteoarthritis in knee and hand both. In serological testing quantitative fasting serum uric acid, C-reactive protein and Rheumatoid factor were performed. In case of bilateral knee joint involvement, knee with more severe involvement was taken for roentgenographic grading. If both knees have similar symptoms and grading, then the radiograph of right knee was included in study. Serum uric acid levels were divided into three groups according to the following distribution of values.

The serum uric acid levels were divided into tertiles.

Group 1: - serum uric acid level less than 5 mg/dl.

Group 2: - serum uric acid level between 5.1 mg/dl-7 mg/dl.

Group 3: - serum uric acid level greater than 7 mg/dl.

For the evaluation of results and to find any association between various entities patients having knee joint osteoarthritis grade 3 and 4 in each uric acid tertile were compared with the patients in the same tertile of uric acid suffering from grade 2 knee joint osteoarthritis. Patients in the third and second tertile were also compared to first tertile for presence of generalized osteoarthritis and knee osteoarthritis. The crude odds ratio (OR) was calculated for the second and third tertiles in comparison to the first tertile. This was then adjusted for age and sex. Mantel-Haenszel stratified analysis method was used for adjustment of odds ratio.

### Results

Out of 340 cases, 225 were males and 115 were females. Knee joint osteoarthritis is present in 238 patients (166 males, and 72 females). Generalized osteoarthritis was seen in 66 patients (43 males, and 23 females). Rheumatoid factor and C-reactive protein were positive in 36 patients. Their distribution among the different serum uric acid tertiles is outlined in Table 2.

**Table1: Patient distribution according to sex and disease**

Patients	Total number(n=340)	Knee Joint Arthritis(n=238)	Generalized Osteoarthritis (n=66)
Males	225	166	43
Females	115	72	23

Association of serum uric acid level with knee osteoarthritis and generalized osteoarthritis was described as odd ratio in table 3. The crude odds ratio was >1 in the association between osteoarthritis of knee, generalized osteoarthritis and the second uric acid tertile [1.05, 1.95] respectively.

After adjusting for age and sex parameters, value of odds ratio was found to be significant for the relationship between the second and third tertile of uric acid level and both osteoarthritis of knee and generalized osteoarthritis [odds ratio-2.31 odds ratio 3.27] respectively.

**Table2: Patient distribution according to Serum uric acid tertiles and radiographic grades of osteoarthritis**

Disease	Uric Acid Tertiles	Kellgren-Lawrence osteoarthritis scale		
		Grade2	Grade3	Grade4
Knee Joint Osteoarthritis(n=225)	<5mg/dl	35	27	23
	5.1-7mg/dl	18	22	25
	>7mg/dl	19	38	31
Generalized Osteoarthritis(n=66)	<5mg/dl	10	7	6
	5.1-7mg/dl	6	7	6
	>7mg/dl	4	8	12
Total		92	109	103

**Table3: The relationship of uric acid tertiles with knee and generalized osteoarthritis expressed as odds ratio**

Disease	Uric acid level	Odds ratio	Adjusted Odds ratio
Knee joint osteoarthritis(n=238)	<5mg/dl	1.00(reference)	1.00(reference)
	5.1-7mg/dl	1.05	1.23
	>7mg/dl	1.00	2.31
Generalized osteoarthritis(n=66)	<5mg/dl	1.00(reference)	1.00(reference)
	5.1-7mg/dl	1.95	2.26
	>7mg/dl	1.00	3.27

There is a strong association present between osteoarthritis of knee joint, generalized osteoarthritis and the highest tertile of serum uric acid level [adjusted odds ratio - 2.31 and adjusted odds ratio- 3.27 respectively]. Also we found a

positive association of increasing serum uric acid with progression of the knee joint osteoarthritis (highest tertile in comparison to lowest tertile of serum uric acid odds ratio- 2.07 (table 4).

**Table 4: Correlation between serum uric acid tertiles and knee osteoarthritis progression expressed as odds ratio(OR)**

Serum uric acid tertiles(mg/dL)	Patients with grade II knee osteoarthritis	Patients with grade III and grade IV knee osteoarthritis	Odds ratio	Odds ratio adjusted for age, and sex
<5mg/dl	35	50	1.00(reference)	1.00(reference)
5.1-7mg/dl	18	47	0.84	0.83
>7mg/dl	19	69	2.25	2.07

**Table 5: Correlation between serum calcium level and knee osteoarthritis**

Serum calcium level (mg/dL)	Grade II knee osteoarthritis	Grade III and IV knee osteoarthritis	Odds ratio	Odds ratio adjusted for age, and sex
<8mg/dl	38	54	1.00(reference)	1.00(reference)
8-11mg/dl	13	41	0.65	0.74
>11mg/dl	21	70	2.17	2.12

**Discussion**

In our study epidemiologic results particularly about greater prevalence of hyperuricemia among male are very much comparable with other previous studies this study also showed an association between hyperuricemia and generalized osteoarthritis as described by various previous studies [8, 9]. This may be explained by the pro-inflammatory effect of the elevated serum uric acid [14]. In a study done by Anna E. Denoblea et al. [15] the strong association of synovial fluid uric acid level with severity of

osteoarthritis of knee joint was advocated. In his study he quantified severity of osteoarthritis radiographically and scintigraphically and concluded that uric acid is a marker of disease severity. He also described strong possibility that uric acid may act as a promoting factor in the pathological process of osteoarthritis by activating the cascade of inflammation. Other possible explanatory mechanisms for the association between high serum uric acid levels and knee OA include genetic predisposition, and endogenous hormonal environment. Etiology of osteoarthritis is still

doubtful but there are many physiological and clinical factors that may contribute to the risk and progression of osteoarthritis. These factors include obesity, joint deformity, trauma, age, and female sex [16]. The increase in both hyperuricemia and osteoarthritis in women after menopause indicate towards any possible hormonal mechanisms. Another Indian study by Mishra et al [17] described correlation of elevated serum uric acid levels with laboratory and anthropometric parameters of various metabolic syndromes. They suggested that this may be due to high caloric diet, sedentary habits and greater prevalence of obesity unfortunately in our study we were unable to find any co-relation in dietary pattern and life style with the elevated serum uric acid level. A co-relation between rise in uric acid level and progression of knee osteoarthritis was also found in present study which is comparable to result of various previous studies [6, 7, 16]. Our study also showed the correlation of serum uric acid level with radiographic severity in knee joint osteoarthritis as measured by Kellgren-Lawrence osteoarthritis scale has been previously reported by Anna E. Denoblea et al [15]. Yazmalar et al [18] found that serum calcium levels were not significantly different between knee osteoarthritis patients and controls.

Our study found inverse relationship between serum calcium concentration and OA of the knee; similar finding also reported by Valhmu WB et al [19] and Kuznetsov G et al [20].

Another reason for the observed association of uric acid level with osteoarthritis of knee joint and generalized osteoarthritis in present study may be that we did not excluded patients already having diabetes and medications including diuretics which have been shown to be associated with osteoarthritis.

### Conclusion

This study supports a possible correlation between hyperuricemia and osteoarthritis. Serum calcium concentration has an inverse relationship with OA of the knee. Various confounding factors such as endogenous hormonal environment, insulin resistance, and genetic predisposition exist, to affect the possible association between hyperuricemia and osteoarthritis. To validate this issue a large sample size multifactorial study is recommended.

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