

ASSOCIATION OF SERUM URIC ACID LEVEL WITH OSTEOARTHRITIS OF  
KNEE JOINT

SAUD A. ABDURRAHMAN, MBChB\*

MOHAMMED T. RASOOL, FRCP (Glasc), FRCP, DMRD (London)\*\*

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**ABSTRACT**

**Background and objectives** Previous studies have shown an association between serum uric acid and generalized osteoarthritis, but the evidence of an association between serum uric acid and knee joint osteoarthritis is limited. The objective of the study is to determine the existence of association between serum uric acid level and osteoarthritis of the knee joint and its significance.

**Methods** A Case-control study was done at rheumatology outpatient clinic at Duhok center for rheumatologic diseases and medical rehabilitation. Two hundred (200) participants aged 31-69 years were recruited; one hundred were patients with unilateral or bilateral knee joint osteoarthritis and 100 were healthy controls. Detailed medical history was obtained at interview. Both patients and controls underwent clinical examination, radiography and fasting blood analysis of uric acid, urea, creatinine, sugar, total cholesterol and triglycerides.

**Results** A significant positive association was found between serum uric acid levels and presence of the knee joint osteoarthritis [highest (third) tertile versus lowest (first) tertile of serum uric acid odd Ratio =4.10, 95% confidence interval (1.73-9.70), P-value < 0.05]. Also a significant positive association was found between serum uric acid levels and progression of the knee joint osteoarthritis [highest (third) tertile versus lowest (first) tertile of serum uric acid odd ratio=2.18, 95% confidence interval (1.03-4.61), P-value < 0.05].

**Conclusion** The results suggest a significant positive association between serum uric acid levels and knee joint osteoarthritis.

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**Key words:** Osteoarthritis, Knee joint, Serum uric acid

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Osteoarthritis (OA) is the most common type of arthritis. Its high prevalence, especially in elderly, and the high rate of disability related to disease makes it a leading cause of disability in the elderly.<sup>1</sup>

The knee is the largest of the human joints in area of articular cartilage and synovial membrane and it is the site of predilection of many diseases including OA, crystal related diseases and inflammatory joint diseases.<sup>2</sup>

Uric acid is the final breakdown product of nucleic acid and purine catabolism in human.<sup>3</sup> Serum uric acid levels are distributed in the community as

a continuous variable and are higher in men than women.<sup>4</sup>

An early epidemiological study reported by Acheson and Collart found that hyperuricemia was significantly associated with OA of multiple joints.<sup>5</sup> A positive association between knee OA and uric acid was found in a study done by university of California in 1988 albeit a small one not reaching significant level.<sup>6</sup>

Serum uric acid relationship with OA was specifically investigated in another study and concluded that although uric acid was associated with generalized OA (GOA) [defined as the simultaneous presence of radiographic changes of knee

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\* Iraqi BOARD student, Department of Internal Medicine, Azadi Hospital, Duhok, Iraq

\*\* Assistant professor of Rheumatology, School of Medicine, Faculty of Medical Sciences, University of Duhok

Correspondence author: Mohammed T. Rasool. Telephone: 07504552497. Email: mzakoly@yahoo.com

and hand OA]<sup>7</sup> in patients undergoing hip replacement, there were no associations with knee OA or bilateral hip and knee OA; the results suggested a possible role of elevated serum uric acid in the multifactorial etiology of GOA.<sup>8</sup>

Other studies accounted for serum uric acid found no association between it and OA,<sup>9,10</sup> while a study done in Saudi Arabia in 1998-1999 found a possible association between hyperuricemia and knee and GOA.<sup>11</sup>

## METHODS

A questionnaire was filled for every patient and control and the patients were examined at the rheumatology outpatient clinic of the Duhok Center for Rheumatologic Diseases and Medical Rehabilitation.

The patients and controls were tested for fasting serum uric acid, blood urea and serum creatinine, fasting blood sugar, fasting serum cholesterol and triglycerides.

Recent x-rays of the knee joints and of other joints that suspected to have OA were inspected. Grading of OA of the knee joint according to radiological findings was done depending on Kellgren and Lawrence grading scheme,<sup>12</sup> (Table 1).

**Table 1. Grading of osteoarthritis of the knee joint according to radiological finding by Kellgren and Lawrence grading scheme**

Grade	Description
Grade 0	Normal
Grade I	Minimal osteophytes, normal joint space
Grade II	Definite osteophytes, possible joint space narrowing
Grade III	Definite osteophytes and joint space narrowing
Grade IV	Definite osteophytes and joint space narrowing with sclerosis and abnormal joint contour

The association between levels of serum uric acid and the presence (versus absence) of the knee OA (unilateral or

bilateral) was assessed. Serum uric acid levels in both groups (cases and controls) were divided into tertiles according to the observed distribution of values (tertile 1 up to 4mg/dl, tertile 2 from 4.1mg/dl to 7mg/dl and tertile 3 above 7mg/dl). The cases in each uric acid tertile were compared to the controls in the same tertile and the crude odd ratio (OR) was calculated for the higher two tertiles in reference to the first (the lowest). This was then adjusted for age, sex, body mass index (BMI), fasting total serum cholesterol and fasting serum triglycerides. The adjustment of OR was done by using Mantel-Haenszel stratified analysis method.<sup>13</sup>

Also the patients having knee joint radiological grades III and IV (advanced OA) in each uric acid tertile were compared to the patients having grades I and II (early OA) in the same tertile. The crude OR was calculated for the higher two tertiles in reference to the first (the lowest) and then adjusted for age, sex, BMI, serum cholesterol and serum triglycerides using Mantel-Haenszel stratified analysis method.

## RESULTS

Distribution of patients and controls according to the uric acid tertiles is shown in table 2. The crude OR was above unity in the relationship between presence of knee OA and the third uric acid tertile (OR 4.73, 95% CI 2.05-10.92, p-value < 0.05).

**Table 2. Distribution of patients and controls according to the uric acid tertiles**

Uric acid tertiles (mg/dl)	Patients (n=100)	Controls (n=100)
1 ( $\leq 4$ )	18	17
2 (4.1-7)	75	82
3 ( $>7$ )	7	1

After adjustment for potential confounding variables (age, sex, BMI, serum cholesterol and serum triglycerides),

the OR did not changed significantly from its crude value (Adjusted OR 4.10, 95% CI 1.73-9.70, p-value < 0.05). This suggests a positive association between third uric acid tertile and presence of knee OA, (Table 3).

The crude OR was above unity in the relationship between advanced knee OA (grades III and IV) and the third uric acid tertile (OR 2.51, 95% CI 1.17-5.38, p-

value < 0.05). Also, adjustment for age, sex, BMI, serum cholesterol and serum triglycerides did not have changed the OR for the third tertile (Adjusted OR 2.18, 95% CI 1.03-4.61, p-value < 0.05). This suggests a positive association between third uric acid tertile and advanced knee OA, (Table 4).

**Table 3. The relationship between serum uric acid tertiles and presence of knee OA expressed as odd ratio (OR) with 95% confidence interval (CI) and p-value**

Uric acid tertiles (mg/dl)	Crude OR (95% CI)	Adjusted OR (95% CI)*
≤ 4	1 (Reference)	1 (Reference)
4.1-7	0.86 (0.62-1.20)	0.85 (0.61-1.19)
> 7	4.73 (2.05-10.92)**	4.10 (1.73-9.70)**

\* Adjusted for age, sex, serum cholesterol, serum, triglycerides and BMI

\*\* Significant results: p < 0.05

CI: Confidence interval

**Table 4. The relationship between serum uric acid tertiles and progression of knee OA expressed as odd ratio (OR) with 95% confidence interval (CI) and p-value**

Uric acid tertiles (mg/dl)	No. of patients with Grades I and II knee OA	No. of patients with Grades III and IV knee OA	Crude OR (95% CI)	Adjusted OR (95% CI)*
≤ 4	12	6	1 (Reference)	1 (Reference)
4.1-7	53	24	0.89 (0.55-1.46)	0.82 (0.50-1.36)
> 7	3	4	2.51 (1.17-5.38)**	2.18 (1.03-4.61)**

\* Adjusted for age, sex, serum cholesterol, serum, triglycerides and BMI

\*\* Significant results: p < 0.05

CI: Confidence interval

## DISCUSSION

This study suggests a significant positive association between serum uric acid levels and both presence and progression of OA of the knee joint. This finding is consistent with a previous study done in Saudi Arabia in 1998-1999 in which a positive

association between serum uric acid level and presence of OA of the knee joint was observed.<sup>11</sup> This may be explained by the pro-inflammatory effect of the elevated serum uric acid.<sup>14</sup> Other possible explanatory mechanisms for the association between high serum uric acid levels and knee OA include genetic

predisposition, and endogenous hormonal environment.<sup>15,16</sup>

Finding such positive association between serum uric acid levels and both presence and progression of OA of the knee joint may make it possible to prevent or slow down the progression of knee joint OA in patients having high serum uric acid level without knee joint OA or having high serum uric acid level in the early stages of knee joint OA by lowering their serum uric acid level with uric acid lowering drugs, the same idea was concluded from the results of a recent research done at Duke University Medical Center.<sup>17</sup>

In this study, 80% of the patients were women which is consistent with that found by the Ulm Osteoarthritis study.<sup>8</sup> Although in our community, this partly may be due to higher number of women than men seeking medical treatment of OA at outpatient clinic, but the increase in OA in women after menopause may point to hormonal mechanism.<sup>16</sup>

Although age, serum cholesterol, serum triglyceride and BMI was found to be associated with OA<sup>1,18-20</sup>; however, these factors as well as gender did not confound the association between serum uric acid, and presence and progression of knee OA. This suggested an association between level of serum uric acid and presence and progression of knee OA.

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## پوخته

## په یوه نډیا ناستی ترشی میزنی دناف خوینیدا دگه ل ناوسانا چوکا

پیشه کی و نارمانج: چند فه کولینین پیشتیر په یوه نډی دیار کریه دنافه را ناستی ترشی میزنی دناف خوینیدا نو ناوسانا گه ها یاههستی یاسه رانسهر، به لی به لگه بو په یوه نډی دنافه را ناستی ترشی میزنی دناف وینیدا دگه ل ناوسانا چوکا یاههستی یی بهر ته نگه. نارمانج ژ فه کولیننی بو دیار کرنا هه بوونا په یوه نډی دنافه را ناستی ترشی میزنی دناف خوینیدا نو ناوسانا چوکا یاههستی دگه ل گرنگیاوی.

ریکین فه کولیننی: نه ف فه کولینه هاته نه نجام دان ل سهر دو سه د (200) پشکداران نه وین ژین وان دنافه را (31-69) سالان دا بوون، سه د (100) ژوان ناوسانا چوکا یاههستی ل لایه کی یان هه رډو لایان هه بوون نه وین دیر سه د (100) که سین ساخلم بوون. میژویا پزشکی ب درژی هاته وه رگرتن ژ پشکداران نو پشکینین سهرجهی ل سهر نه وان هاتنه کرن، هه روه سا پشکینین تیشکی، ناستین ترشی میزنی، یوریا، کریاتینین، شه کر، کولیسترول گشتی نو چه ورین سیانی دناف خوینیدا هاتنه وه رگرتن.

نه نجام: په یوه نډی په پوسیتیف و گرنگ هاته دیتن دنافه را ناستی ترشی میزنی دناف خوینیدا نو هه بوونا ناوسانا چوکا یاههستی (ریژا جیاوازی) (odds ratio) بو به رز ترین (سینیه مین) سینیه که به رامبه ر نزمترین (نیکه مین) سینیه که 4.1، نافرا باوه ریی (confidence interval) (1.73-9.70)، به های پ-value ژ 0.05 کیمتر بو، هه روه سا په یوه نډی په پوسیتیف و گرنگ هاته دیتن دنافه را ناستی ترشی میزنی دناف خوینیدا نو پیشفه چوونا ناوسانا چوکا یاههستی (ریژا جیاوازی) بو به رزترین (سینیه مین) سینیه که به رامبه ر نزمترین (نیکه مین) سینیه که 2.18، نافرا باوه ریی (confidence interval) (1.03-4.61)، به های پ-value ژ 0.05 کیمتر بو.

دوره نه نجام: نه نجامین فه کولیننی ناماژه دکن کو په یوه نډی په پوسیتیف و گرنک هه یه دنافه را ناستی ترشی میزنی دناف خوینیدا نو ناوسانا چوکا یاههستی.

## الخلاصة

## العلاقة بين مستوى الحامض البولي في الدم وإلتهاب المفصل العظمي لمفصل الركبة

**خلفية واهداف البحث:** أظهرت دراسات سابقة وجود علاقة بين مستوى الحامض البولي في الدم و إلتهاب المفاصل العظمي المعمم. لكن الدليل حول وجود علاقة بين مستوى الحامض البولي في الدم و إلتهاب مفصل الركبة العظمي لوحده محدود. الهدف من البحث هو للتأكد من وجود أية علاقة بين مستوى الحامض البولي في الدم وإلتهاب المفصل العظمي للركبة ومدى أهميتها من الناحية الإحصائية.

**طرق البحث:** دراسة من نوع حالة - سيطرة ( Study Case-Control ) أجريت في مركز دهوك لأمراض المفاصل و التأهيل الطبي على مائتي (200) مشارك تراوحت أعمارهم بين 31-69 سنة. مائة(100) منهم كانوا مصابين بالتهاب المفصل العظمي للركبة في طرف واحد أو في الطرفين و المائة (100) الباقية كانوا أصحاء (غير مصابين بالتهاب المفصل العظمي للركبة). تم أخذ التاريخ الطبي المفصل من المشاركين و أجري عليهم الفحص السريري مع أخذ الفحص الشعاعي و الفحوصات المختبرية لقياس مستوى الدم لكل من الحامض البولي، اليوريا، الكرياتينين، السكر، الكولسترول الكلي و الدهون الثلاثية.

**النتائج:** وجدت علاقة إيجابية ذات أهمية إحصائية بين الحامض البولي في الدم و وجود إلتهاب مفصل الركبة العظمي(نسبة الأرجحية ( odd Ratio ) للثلث الأعلى ضد الثلث الأدنى للحامض البولي في الدم = 4.10، 95% فاصل الثقة (Confidence Interval) 1.73-9.70، قيمة p-value أقل من 0.05). كما وجدت علاقة إيجابية ذات أهمية إحصائية بين الحامض البولي في الدم و تقدم إلتهاب مفصل الركبة العظمي (نسبة الأرجحية للثلث الأعلى ضد الثلث الأدنى للحامض البولي في الدم = 2.18، 95% فاصل الثقة 1.03-4.61، قيمة p-value أقل من 0.05).

**الاستنتاج:** النتائج تقترح وجود علاقة إيجابية ذات أهمية إحصائية بين مستوى الحامض البولي في الدم و إلتهاب مفصل الركبة العظمي.