

# Association between Asymptomatic Hyperuricemia and Knee Osteoarthritis

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**Abstract:** **Background:** knee osteoarthritis is one of the most prevalent chronic conditions in older individuals which impairs function, negatively impacts quality of life, and can occasionally result in disability. One metabolic condition that is frequently discovered in older persons is asymptomatic hyperuricemia. Research has indicated that asymptomatic hyperuricemia is also prevalent in patients with knee osteoarthritis. The two disorders are believed to be pathophysiologically connected due to cartilage destruction brought on by uric acid, and they share some risk factors, such as advanced age and increase in Body Mass Index (BMI). **Objective:** To explore the relationship between asymptomatic hyperuricemia and knee osteoarthritis among Iraqi Hospital outpatients. **Patients and Methods:** This cross-sectional study included 250 Iraqi outpatients (125 patients with knee osteoarthritis and 125 individuals without knee osteoarthritis) aged (40 - 80 years (mean age  $52.51 \pm 7.71$  years) visiting rheumatologic outpatient clinic at Baghdad Teaching Hospital from December 2023 until September 2024. Data from both groups' were collected, including demographics, symptoms and signs of knee osteoarthritis, serum uric acid levels, and knee radiographs. The correlation between asymptomatic hyperuricemia and knee osteoarthritis was investigated using logistic regression. **Results:** patients with knee osteoarthritis had a higher mean serum uric acid level compared to individuals without knee osteoarthritis ( $5.98 \pm 1.34$  mg and  $4.99 \pm 1.05$  mg  $P < 0.001$ ) respectively. The prevalence of hyperuricemia was higher in older outpatients with knee osteoarthritis than in those without knee osteoarthritis (30.4% vs. 5.6%,  $p < 0.001$ ). Asymptomatic hyperuricemia and knee osteoarthritis were still significantly associated after controlling for age, sex, body mass index (BMI), and other comorbidities (odds ratio [OR] 3.17, 95% confidence interval [CI] 2.18 - 6.99,  $p = 0.007$ ). Subgroup analyses based on BMI and sex categories were conducted and revealed a significant association between asymptomatic hyperuricemia and knee osteoarthritis among men and women ( $p < 0.001$  and  $p < 0.004$ ) respectively, and among individuals who were normal - weight and obese according to BMI ( $p = 0.009$  and  $p < 0.001$ ) respectively. **Conclusions:** Asymptomatic hyperuricemia is one of the most prevalent comorbidities among elderly outpatients with knee osteoarthritis. Among Iraqi outpatients, an independent correlation between asymptomatic hyperuricemia and knee osteoarthritis was noted; however, this correlation may be influenced by confounding variables such as sex and BMI.

**Keywords:** Asymptomatic hyperuricemia, Knee Osteoarthritis, Risk Factors, Serum Uric acid

## 1. Introduction

Osteoarthritis (OA) is the most common degenerative disorder and is traditionally characterized by clinical symptoms such as joint pain and stiffness as well as radiographic changes including joint space narrowing and osteophyte formation. OA is markedly associated with increased health burden and mortality (1). 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. The knee is the largest of the human joints in areas 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 (2). Also it is the most common type of arthritis worldwide a painful and debilitating condition for which no disease modifying therapy currently exists (3). Although OA was historically regarded as a disease of mechanical degeneration, it is now recognized that inflammation plays an important role in its pathogenesis (4). As 1 of the 5 leading causes of disability among non-institutionalized adults, knee OA is usually a slowly progressing disease, whereas some patients show more rapid progression leading to severe joint damage (5).

## Prevalence

OA is the leading cause of arthritis in the world affecting (10 - 15%) of adults, with a lifetime risk as high as 50% (6). About 13% of women and 10% of men aged 60 years and older have symptomatic knee OA. The proportions of people affected with symptomatic knee OA is likely to increase due to the aging of the population and the rate of obesity or overweight in the general population (7).

## Etiology

OA is markedly associated with increased health burden and mortality. Diverse pathogenic mechanisms in the development and progression of OA consist of mechanical stress, inflammatory responses, metabolic disturbances, and genetic predisposition, although the different degrees to which of these contribute to OA in a given individual (1). Knee OA is classified as either primary (idiopathic) or secondary. Among the various structures making up the knee joint, the hyaline joint cartilage is the main target of the harmful influences that cause osteoarthritis. The main causes of secondary osteoarthritis of the knee are either endogenous causes, which includes: age, sex, heredity, ethnicity, and post-menopausal women or exogenous causes, which includes: macrotrauma, repetitive microtrauma, overweight

resective joint surgery, life style factors (alcohol and smoking (8).

**Risk factors**

OA has a multifactorial etiology, with different set of factors with its incidence. While considering non - modifiable factors for OA are age and sex is the strongest predictors. For example, women is higher risk than male, above 40 years age group is vulnerable for OA. Considering modifiable risk factors are occupation, dietary factors, obesity and physical activity. OA is common in those who performing heavy physical work, especially if those involves knee bending, squatting or kneeling. Obesity is a strong modifiable risk factor. House wife, workers, those who work prolonged standing is the predominant risk group. Factors associated with OA could also interact in complex way (9).

**Diagnosis**

Pain, stiffness, and locomotor restriction are the main symptoms of OA. Other symptoms include crepitus, joint deformity, or joint swelling (caused by bony remodeling, excessive osteophytosis, or joint subluxation). These symptoms typically begin in just 1 or a few joints in a person of middle or older age. Pain which worsen with joint use and that relieved by rest (usage or mechanical pain) is often the most troublesome symptom (9). The American College of Rheumatology (ACR) classification criteria for OA of the knee were used widely (10). Plain radiography remains a mainstay in the diagnosis of OA. The first formalized attempts at establishing a radiographic classification scheme for OA were described by Kellgren and Lawrence (KL) in 1957 (11). In 1968, Ahlbäck showed the advantage of standing radiographic examinations to demonstrate the presence of knee OA (12). The original definitions of the KL scale, Ahlbäck classification are shown in Table (1).

**Table 1:** Comparison of the original definitions of the Kellgren–Lawrence (KL) scale, Ahlbäck clasScheme (13)

Grade	KL Scale	Ahlbäck Classification
Grade 0	No pathological features of osteoarthritis (OA)	
Grade 1	Suspicious narrowing of the joint space and possible osseous lip	Joint space narrowing, with or without subchondral sclerosis. Joint space narrowing is defined by this system as a joint space <3 mm, or less than half of the space in the other compartment, or less than half of the space of the homologous compartment of the other knee
Grade 2	Clear bone tissue and possible stenosis of the joint space	Obliteration of the joint space
Grade 3	Moderate multiple bone tissue, clear narrowing of the joint space, slight sclerosis, and possible deformity of the ends of the bones	Bone defect/loss < 5 mm
Grade 4	Large bone tissue, marked narrowing of the joint space, severe sclerosis, and clear deformities of the ends of the bones	Bone defect/loss between 5 mm and 10 mm
Grade 5		Bone defect/loss >10 mm, often with subluxation and arthritis of the other compartment

KL scale: Kellgren - Lawrence scale, OA: osteoarthritis.

**Treatment**

Currently, various guidelines have been developed to standardize and recommend available treatments by

academic and professional societies. Table (2) shows the available treatment options from the Osteoarthritis Research Society International (OARSI), ACR (14, 15).

**Table 2:** Osteoarthritis of the knee management recommendations from the two societies. (16)

Treatment	OARSI	ACR
Exercise (Land - based)	Appropriate	Strong recommendation
Exercise (Water - based)	Appropriate	Strong recommendation
Transcutaneous electrical nerve stimulation	Uncertain	Strong recommendation against use
Cane (Walking stick)	Appropriate	Strong recommendation
Weight control	Appropriate	Strong recommendation
Chondroitin or Glucosamine	Not appropriate for disease modification, Uncertain (Sx relief)	Strong recommendation against use
Acetaminophen	Without comorbidities: appropriate	Conditional recommendation
Duloxetine	Appropriate	Conditional recommendation
Oral NSAIDs	Without comorbidities: appropriate; With comorbidities: Uncertain	Strong recommendation
Topical NSAIDs	Appropriate	Conditional recommendation against use
Opioids	Uncertain	No recommendation
Intra - articular corticosteroids	Appropriate	Strong recommendation
Intra - articular viscosupplementation	Uncertain	Conditional recommendation against use

OARSI: Osteoarthritis Research Society International; ACR: American College of Rheumatology; NSAIDs: non - steroidal anti - inflammatory drugs.

## Asymptomatic Hyperuricemia

### Definition:

Asymptomatic HU is defined as the presence of serum hyperuricemia in the absence of gout, tophi or urate nephropathy/uroolithiasis (17). Asymptomatic HU is a common metabolic disorder diagnosed among older adults, and some studies have shown that asymptomatic HU is common among patients with knee OA (18).

The two conditions share some risk factors, such as increased age and Body Mass Index (BMI) and are thought to be pathophysiologically related through cartilage damage caused by uric acid. At high concentrations, uric acid can form deposits in the articular cartilage, causing local mechanical damage and activating inflammatory reactions, leading to the destruction of joint cartilage (19)

HU was recently defined as serum uric acid above 7.7 mg/dl in men and above 6.6mg/dl in women (20), or above 7.0 mg/dl in men and above 5.7 (21) or 6 mg/dl in women (22). Asymptomatic HU was defined as serum uric acid levels  $\geq 6.8$  mg/dl with no prior gout flares or subcutaneous tophi (17).

### Prevalence

The prevalence of asymptomatic HU in the United states (US) has been increasing and is approximately 17.6%, significantly higher than the prevalence of gout (3.9%) (22). Asymptomatic HU in individuals who have not experienced gout nor nephrolithiasis, is viewed as a non - pathological condition whilst its prevalence is estimated to range between 10% and 20% worldwide (23).

### Treat or do not treat

Treatment of asymptomatic HU is not necessary in most patients, unless perhaps they have very high levels of uric acid or are otherwise at risk of complications, such as those with a personal or strong family history of gout, urolithiasis, or uric acid nephropathy (24).

Also ACR recommends that: - "For patients with asymptomatic hyperuricemia (SU  $>6.8$  mg/dl with no prior gout flares or subcutaneous tophi), we conditionally recommend against initiating any pharmacologic ULT (allopurinol, febuxostat, probenecid)" (17)

### Aim of study

This study attempt to investigate the possible association between asymptomatic HU and knee OA in Iraqi patients as some studies have documented such an association.

### Patients and methods

#### Study design and population

This cross sectional observational study was done at Baghdad Teaching Hospital/ Medical City complex - Baghdad/Iraq, from February 2024 until September 2024.

The study population consisted of 250 individuals (125 osteoarthritic and 125 healthy individuals served as controls) sample of individuals aged 40 - 80 years. Patients were

diagnosed with knee osteoarthritis by fulfilling the clinical A C R criteria of OA (25)

- 1) Typical signs and symptoms of knee osteoarthritis.
- 2) Their diagnosis are confirmed by clinical examination and Knee x - ray.
- 3) Patients can participate and cooperate with this research work.

### Exclusion criteria:

- Previous knee injury or knee surgery
- Patients with past medical history of gout, rheumatoid arthritis, chronic kidney disease.
- Patients who take medications known to cause hyperuricemia (diuretics, cyclosporine, pyrazinamide, ethambutol, aspirin) used during the past two weeks.
- Patients with history of mental illnesses who cannot participate in this study.

## 2. Data Collection

After attaining the criteria and agreement to participate in the study, the following data for each participant were reported:

- Sociodemographic data, including the (name, age, sex, place of residence, marital status, level of education, type and duration of work, praying, using stairs, type of W/C used whether eastern or western).

The body weight was measured in kilograms (kg) and the height was measured in meters (m) using a stadiometer. The body mass index (BMI) was then calculated using the following equation:

**BMI= weight in kilograms divided by the squared height in meters.**

Participants were then categorized according to the WHO classification system, in which BMI  $< 18.5$  kg/m<sup>2</sup> is underweight, BMI range 18.5 - 24.9 kg/m<sup>2</sup> is normal, ranges of 25 - 29.9 kg/m<sup>2</sup> are considered overweight and BMI between 30 - 34.9 kg/m<sup>2</sup> as obesity class 1, BMI range 35 - 39.9 kg/m<sup>2</sup> is obesity class 2, above 40 kg/m<sup>2</sup> is obesity class 3 (26).

- The following Past medical history of patients are documented if they have:

(Hypertension, Diabetes mellitus, Ischemic heart disease and Asthma).

#### a) Knee osteoarthritis symptoms were documented as:

- Knee pain.
- Morning stiffness  $<30$  min.
- Knee swelling.

#### b) Knee osteoarthritis signs were documented after knee joint clinical examination as:

- Knee joint line tenderness.
- limitation of knee joint motion.
- Presence of bone hypertrophy.
- Presence of crepitations.
- Presence of knee joint deformities.
- Presence of Popliteal cyst.
- Presence of fluid.

c) **Knee joint osteoarthritis was diagnosed by x - ray according to kellgren - lawrence scale:**

- Presence of osteophytes.
- Presence of decrease in joint space.
- Presence of subchondral cysts.
- Presence of subchondral sclerosis.

**The skeleton of questionnaire was built by the researchers.**

**Measuring serum uric acid level:**

Serum uric acid levels were measured by (Selectra pro XI) at Laboratory Department/ Baghdad Teaching Hospital and were reported in (mg/dl).

**Ethical consideration:**

Ethical approval was obtained from the Iraqi Board of Medical Specializations after submission of the research protocol, in accordance with the Declaration of Helsinki and this is documented in the administrative order number **642** in the **31<sup>st</sup> of January 2024**. An informed and signed consent was obtained from each participant included in the study.

**Statistical analysis:**

The data were analyzed statistically using SPSS (version 29). A detailed descriptive statistics were used to outline the means and standard deviations.

The frequencies and percentages were used to describe categorical variables.

Regarding inferential statistics, student's t test was used to identify the differences in means and standard deviations among different study groups.

Chi - square test and Fishers exact test were used as appropriate for categorical variables to identify differences in frequencies in study groups.

P value below 0.05 was considered statistically significant.

### 3. Results

**Demographics and characteristics of the study population**

This study included a total sample of 250 candidates, 125 (50%) of them had knee OA, while 125 (50%) of them had no knee OA. The mean and standard deviation ( $M \pm SD$ ) of those with and without OA were  $55.46 \pm 8.71$ , and  $49.57 \pm 5.09$  respectively with significant difference ( $P < 0.001$ ); 118 (47.2%) were males, while 132 (52.8%) were females, and their distribution according to OA status was 44 (35.2%) males and 81 (64.8%) females with OA, and 74 (59.2%) males and 51 (40.8%) females without OA, with a significant differences ( $P < 0.001$ ) between OA patients and individuals without OA .

According to body mass index (BMI), among those with knee OA, obese individuals made the majority 77 (61.6%) while overweight and normal weight individuals comprising 37 (29.6%) and 11 (8.8%) respectively, for individuals without knee OA, overweight individuals was reported among 47 (37.6%), normal weight and obese individuals were comprising 51 (40.8%) and 27 (21.6%) respectively

with a significant differences ( $P < 0.001$ ) between OA patients and individuals without OA.

According to education level, among those with knee OA, 10 (8.0%) were illiterate, 47 (37.6%) of them achieved primary school, 23 (18.4%) of them achieved secondary school, 27 (21.6%) of them achieved institute, 18 (14.4%) of them achieved bachelor and above, while candidates without knee OA, 2 (1.6%) of them were illiterate, 17 (13.6%) of them achieved primary school, 45 (36.0%) of them achieved secondary school, 36 (28.8%) of them achieved institute, 25 (20.0%) of them achieved bachelor and above with a significant differences ( $P < 0.001$ ) between OA patients and individuals without OA.

Residence status, patients with knee OA, urban made the majority with 103 (82.4%), 22 (17.6%) were rural, while among those without knee OA, 99 (79.2%) were urban, 26 (20.8%) were rural with no significant differences between OA patients and individuals without OA.

The marital status of individuals with knee OA, married persons made the majority 68 (54.4%), 47 (37.6%) were widowed, 6 (4.8%) were divorced and 4 (3.2%) were single, while individuals without knee osteoarthritis OA,, married persons made the majority 102 (81.6%),, 13 (10.4%) were widowed, 8 (6.4%) were single and 2 (1.6%) were divorced with a significant difference ( $p < 0.001$ ) between OA patients and individuals without OA.

Type of work among knee OA patients, housewives made the majority of them 63 (50.4%), 28 (22.4%) were manual laborers, 22 (17.6%) were teachers, 10 (8%) with sedentary work (clerk, computer work) while 2 (1.6%) patients were engineers,, compared to those without knee OA, 13 (10.4%) with sedentary work (clerk, computer work), also housewives made the majority of them 43 (34.4%), 35 (28.0%) were manual workers, 30 (24%) were teachers, and 4 (3.2%) were engineer, without significant differences between OA patients and individuals without OA.

According to work duration, patients with knee OA, patients with occupation duration  $> 10$  years comprised 105 (84.0%), while patients with (6 - 10) years duration and (1 - 5) years duration were comprised 14 (11.2%) and 6 (4.8%) respectively, in an other hand, individuals without knee OA, 1 (0.8%) with (1 - 5) years duration, 29 (23.2%) with (6 - 10) years duration, 95 (76.0%) with  $> 10$  years with a significant differences ( $p 0.008$ ) between OA patients and individuals without OA.

The serum UA levels for the knee OA group and the group without knee OA ( $5.98 \pm 1.34$  mg and  $4.99 \pm 1.05$  mg) respectively with a significant difference ( $P < 0.001$ ) between them. The percentage of individuals who have asymptomatic HU was significantly higher in the knee OA group in comparison to the non - knee OA group (69.6%) vs. (94.4%) respectively with a significant differences ( $P < 0.001$ ) between OA patients and individuals without OA.

According to way of sitting during praying, patients with knee OA, 121 (96.8%) of them were prayers, 4 (3.2%) of them don't pray,, while among those without knee OA, 123



(98.4%) were prayer, 2 (1.6%) don't pray, with no significant differences between OA patients and individuals without OA.

Using stairs, patients with knee OA who experienced pain and numbness while using stairs, 36 (28.8%) of them use stairs, 89 (71.2%) don't use stairs, while participants without knee OA, 79 (63.2%) use stairs, 46 (36.8%) don't use stairs, with a significant difference (P <0.001) between OA patients and individuals without OA.

Using eastern W/C, patients who have knee OA, 9 (7.2%) of them use eastern W/C, 116 (92.8%) of them don't use eastern W/C, while individuals without knee OA, 14 (11.2%) do not use eastern W/C, 111 (88.8%) of them use eastern W/C, with significant differences (p<0.001) between OA patients and individuals without OA.

Comorbidities: hypertension, patients who have knee OA, 71 (56.8%) of them were hypertensive and 54 (43.2%) were not hypertensive, while individuals without knee osteoarthritis, 16 (12.8%) of them have hypertension and 109 (87.2%) have no hypertension, with a significant difference (P <0.001) between OA patients and individuals without OA.

Patients with history of Diabetes Mellitus (DM) who have knee OA were 42 (33.6%) and 83 (66.4%) have no (DM),

while individuals without knee osteoarthritis, 7 (5.6%) of them have DM and 118 (94.4%) have no DM and, with a significant difference (P <0.001) between OA patients and individuals without OA.

Patients who have knee OA, 19 (15.2%) of them have Ischemic Heart Disease (IHD) and 106 (84.8%) of them have no IHD, while individuals without knee OA, 3 (2.4%) of them have IHD and 122 (97.6%) of them have not IHD, with a significant difference (P = 0.003) between OA patients and individuals without OA.

Patients who have knee OA, 117 (93.6%) of them have no asthma, 8 (6.4%) had asthma, while among those without knee OA, 123 (98.4%) had no asthma, 2 (1.6%) had asthma, with no significant difference between OA patients and individuals without OA.

Smoking status, among individuals who have knee OA, 50 (40.0%) never smoked, 41 (32.8%) were past smokers, 34 (27.2%) were current smokers, while individuals without knee OA, 88 (70.4%) never smoked, 14 (11.2%) were past smokers, 23 (18.4%) were current smokers, so smoking is significantly associated with knee osteoarthritis (P <0.001) between OA patients and individuals without OA. All these results are shown in table (3 - A &B):

**Table (3 - A):** Baseline characteristics of participants

Variables	Non - Knee osteoarthritis individuals (n = 125)	Knee Osteoarthritis Patients (n = 125)	All (n = 250)	p - value
<b>Age (years) / M± SD</b>	49.57± 5.09	55.46± 8.71	52.51± 7.71	<0.001
<b>Sex n (%)</b>				
Male	74 (59.2%)	44 (35.2%)	118 (47.2%)	<0.001
Female	51 (40.8%)	81 (64.8%)	132 (52.8%)	
<b>BMI</b>	27.10± 3.14	31.20± 4.23	29.15± 4.25	<0.001
<b>BMI groups n (%)</b>				
Normal	47 (37.6%)	11 (8.8%)	58 (23.2%)	<0.001
Overweight	51 (40.8%)	37 (29.6%)	88 (35.2%)	
Obese	27 (21.6%)	77 (61.6%)	104 (41.6%)	
<b>Level of education, n (%)</b>				
Illiterate	2 (1.6%)	10 (8.0%)	12 (4.8%)	<0.001
Primary school	17 (13.6%)	47 (37.6%)	64 (25.6%)	
Secondary school	45 (36.0%)	23 (18.4%)	68 (27.2%)	
Institute	36 (28.8%)	27 (21.6%)	63 (25.2%)	
Bachelor and above	25 (20.0%)	18 (14.4%)	43 (17.2%)	
<b>Residence, n (%)</b>				
Urban	99 (79.2%)	103 (82.4%)	202 (80.8%)	0.52
Rural	26 (20.8%)	22 (17.6%)	48 (19.2%)	
<b>Marital status, n (%)</b>				
Single	8 (6.4%)	4 (3.2%)	12 (4.8%)	<0.001
Married	102 (81.6%)	68 (54.4%)	170 (68.0%)	
Divorced	2 (1.6%)	6 (4.8%)	8 (3.2%)	
Widowed	13 (10.4%)	47 (37.6%)	60 (24.0%)	
<b>Type of work n (%)</b>				
Sedentary (clerk, computer work)	13 (10.4%)	10 (8%)	23 (9.2%)	0.15
Housewife	43 (34.4%)	63 (50.4%)	106 (42.4%)	
Teacher	30 (24%)	22 (17.6%)	52 (20.8%)	
Engineer	4 (3.2%)	2 (1.6%)	6 (2.4%)	
Manual laborer	35 (28.0%)	28 (22.4%)	63 (25.2%)	
<b>Work duration</b>				
1 - 5 years	1 (0.8%)	6 (4.8%)	7 (2.8%)	0.008
6 - 10 years	29 (23.2%)	14 (11.2%)	43 (17.2%)	
> 10 years	95 (76.0%)	105 (84.0%)	200 (80.0%)	

M: Mean, SD: Standard deviation, BMI: Body Mass Index, N: numbers, P - value: probability value (<0.05) significant, % percent.

**Table (3 - B):** Baseline characteristics of participants

Variables	Non - Knee osteoarthritis individuals (n = 125)	knee osteoarthritis patients (n = 125)	All (n = 250)	p - value
<b>SUA level</b>	4.99±1.05	5.98± 1.34	5.49± 1.30	<0.001
<b>SUA grade</b>				
Normal	118 (94.4%)	87 (69.6%)	205 (82.0%)	<0.001
Hyperuricemia	7 (5.6%)	38 (30.4%)	45 (18.0%)	
<b>Praying</b>				
No	2 (1.6%)	4 (3.2%)	6 (2.4%)	0.68
Yes	123 (98.4%)	121 (96.8%)	244 (97.6%)	
<b>Using stairs</b>				
No	46 (36.8%)	89 (71.2%)	135 (54.0%)	<0.001
Yes	79 (63.2%)	36 (28.8%)	115 (46.0%)	
<b>Eastern W/C</b>				
No	14 (11.2%)	116 (92.8%)	130 (52%)	<0.001
Yes	111 (88.8%)	9 (7.2%)	120 (48%)	
<b>Western W/C</b>				
No	110 (88.0%)	17 (13.6%)	127 (50.8%)	<0.001
Yes	15 (12.0%)	108 (86.4%)	123 (49.2%)	
<b>Comorbidities</b>				
<b>Past medical history of HT</b>				
No	109 (87.2%)	54 (43.2%)	163 (65.2%)	<0.001
Yes	16 (12.8%)	71 (56.8%)	87 (34.8%)	
<b>Past medical history of DM</b>				
No	118 (94.4%)	83 (66.4%)	201 (80.4%)	<0.001
Yes	7 (5.6%)	42 (33.6%)	49 (19.6%)	
<b>Past medical history of IHD</b>				
No	122 (97.6%)	106 (84.8%)	228 (91.2%)	<0.003
Yes	3 (2.4%)	19 (15.2%)	22 (8.8%)	
<b>Past medical history of Asthma</b>				
No	123 (98.4%)	117 (93.6%)	240 (96.0%)	0.053
Yes	2 (1.6%)	8 (6.4%)	10 (4.0%)	
<b>History of smoking</b>				
Never	88 (70.4%)	50 (40.0%)	138 (55.2%)	<0.001
Past	14 (11.2%)	41 (32.8%)	55 (22.0%)	
Current	23 (18.4%)	34 (27.2%)	57 (22.8%)	

SUA: Serum Uric Acid, W/C: water closet, HT: Hypertension, DM: Diabetes Mellitus, IHD: Ischemic Heart Disease, N: numbers, P - value: probability value (<0.05) significant, % percent.

**Logistic regression analysis with knee osteoarthritis as the outcome variable.**

Regression analysis was conducted on the different independent variables to calculate the odd ratio (OR) of having OA as a dependent variable.

Asymptomatic hyperuricemia OR was 3.17 with a significant difference (P 0.007). Sex OR was 2.94 with a significant difference (P = 0.001). Age OR was 1.20 with a significant difference (0.005).

Marital status, level of education, praying, using stairs and type of W/C were without significant difference.

Hypertension and diabetes mellitus were common variables recognized in this study with OR and significant difference (6.61), (p=0.01) and (8.21), (p=0.001) respectively. IHD and Asthma OR were 3.19 and 1.16 with no significant differences.

Smoking as a whole was significantly associated with knee OA, with OR of 4.13 comparing those who never smoke

with those who smoked in the past (P= 0.004), and OR of 3.85 of comparing those who never smoked with those who are current smokers (P = 0.01). These results are shown in table 4.

**Table 4:** Logistic regression analysis with knee osteoarthritis as the outcome variable

Variable	OR	95% CI		P value
		Lower	Upper	
<b>Asymptomatic hyperuricemia</b>	3.17	2.18	6.99	0.007
<b>Sex</b>	2.94	1.97	8.47	0.001
<b>Age</b>	1.20	1.06	1.36	0.005
<b>BMI groups</b>				0.06
Overweight	2.09	0.44	10.07	0.36
Obese	6.73	1.23	36.89	0.03
<b>Marital status</b>				0.81
Married	0.89	0.09	9.13	0.92
Divorced	0.73	0.02	24.37	0.86
Widowed	2.09	0.15	28.94	0.58
<b>Education level</b>				0.61
Primary school	6.37	0.34	11.02	0.21
Secondary school	3.16	0.14	6.16	0.47

Institute	2.07	0.08	5.47	0.66
Bachelor and above	1.35	0.03	4.38	0.87
Praying	0.04	0.02	2.11	0.37
Using Stairs	6.21	3.49	8.95	<0.001
Using eastern W/C	2.00	0.11	5.87	0.64
Using western W/C	1.01	0.12	7.35	0.99
HT	6.61	1.79	8.23	0.01
DM	8.21	3.52	12.82	0.001
IHD	3.19	0.25	5.18	0.37
Asthma	1.16	0.07	3.29	0.92
Smoking				0.01
Past	4.13	3.28	5.66	0.004
Current	3.85	2.79	4.19	0.01

OR: Odd Ratio, CI: Confidence Interval, BMI: Body Mass Index, SUA: Serum Uric Acid, W/C: water closet, HT: Hypertension, DM: Diabetes Mellitus, IHD: Ischemic Heart Disease, P - value: probability value (<0.05) significant.

**Calculating asymptomatic hyperuricemia incidence in patients with and without knee osteoarthritis according to sex difference**

A subgroup statistical analysis according to sex declared that serum uric acid levels and the percentage of candidates experiencing asymptomatic hyperuricemia were significantly higher among males and females in the knee osteoarthritis than among males and females in the non - knee osteoarthritis group (p=<0.001).

**Logistic regression analysis with knee osteoarthritis as the outcome variable in female patients.**

Regression analysis was conducted on the different independent variables among females only to calculate the OR of having OA as a dependent variable.

After taking associated elements into account, such as (Age, BMI and D. M) this study found a significant association between asymptomatic hyperuricemia and knee osteoarthritis among women with asymptomatic hyperuricemia increasing the likelihood of knee osteoarthritis OR 2.43 (P=0.03) as shown in table (5):

**Table 5:** Logistic regression analysis with knee osteoarthritis as the outcome variable in female patients

Characteristics	OR	(95% CI)		p - value
		Lower	Upper	
Asymptomatic HU	2.43	1.05	3.11	0.03
Age	1.12	1.05	1.28	0.14
BMI groups				0.03
Normal	4.13	1.33	12.83	0.014
Overweight - obese	7.45	6.15	11.50	<0.001
Pray	2.74	1.02	3.24	1.000
Stairs	11.48	4.75	27.71	0.07
Eastern w/c	5.97	0.70	51.11	0.10
Western w/c	3.44	0.56	21.17	0.18
HT	5.61	3.52	6.32	0.91
DM	3.71	1.66	9.18	0.02
IHD	1.01	0.33	4.63	0.58
Asthma	1.04	1.02	2.73	0.78

OR: Odd Ratio, CI: Confidence Interval, BMI: Body Mass Index, HU: Hyperuricemia, W/C: water closet, HT: Hypertension, DM: Diabetes Mellitus, IHD: Ischemic Heart Disease, P - value: probability value (<0.05) significant.

**The relation of asymptomatic hyperuricemia according to BMI in osteoarthritis and non - osteoarthritis individuals:**

In subgroup analysis according to BMI groups revealed that serum uric acid levels and the percentage of individuals having asymptomatic hyperuricemia were significantly higher among osteoarthritic patients who were overweight or obese and diagnosed with knee osteoarthritis than among overweight or obese candidates without knee osteoarthritis (p=<0.001). However, these associations were also significant but to a lesser extent among normal weight individuals with and with out knee osteoarthritis compared to overweight and obese candidates with and without knee OA (p=0.003).

**Association between asymptomatic hyperuricemia and knee osteoarthritis in normal - weight candidates group:**

After modification of related factors, such as age, sex a significant association was identified between asymptomatic hyperuricemia and knee osteoarthritis among normal - weight individuals. Normal - weight individuals with asymptomatic hyperuricemia had a higher probability to be diagnosed with knee osteoarthritis with an odd ratio of (9.66) as it is shown in table (6).

**Table 6:** Logistic regression analysis with knee osteoarthritis as the outcome variable in the normal BMI group

Characteristics	OR	(95% CI)		p - value
		Lower	Upper	
Asymptomatic HU	9.66	2.13	43.71	0.01
Age	1.24	1.11	1.38	<0.001
Sex	2.95	1.78	13.53	<0.001
Pray	0.08	0.001	5.31	0.24
Stairs	4.79	2.24	8.93	<0.001
Eastern W/C	3.67	0.221	6.88	0.365
Western W/C	1.47	0.177	2.16	0.722
HT	1.06	0.77	4.17	0.001
DM	5.71	5.60	13.65	<0.001
IHD	3.28	0.31	5.23	0.33
Asthma	1.20	0.12	2.32	0.88

OR: Odd Ratio, CI: Confidence Interval, BMI: Body Mass Index, HU: Hyperuricemia, W/C: water closet, HT: Hypertension, DM: Diabetes Mellitus, IHD: Ischemic Heart Disease, P - value: probability value (<0.05) significant.

**4. Discussion**

To the best of our knowledge, this is the first study conducted in Baghdad City to assess the possible association between asymptomatic hyperuricemia and knee osteoarthritis among adults older than 40 years presenting to outpatient clinic in Baghdad Teaching Hospital.

The mean age of participants in this study was (55.46±8.71 and 49.57±5.09) in participants with knee osteoarthritis and without osteoarthritis respectively, Cao et al (4) found that the mean age of participants were (73.64 ± 8.14 and 72.26 ± 7.32) in participants with knee osteoarthritis and without osteoarthritis respectively. While the median age of population in the United Kingdm is 40 years compared to 32.9 years in Vietnam and 20.6 in Iraq (27).

These differences can be explained by the variation in the median ages of populations studied as mentioned above, and range of age of samples, in our study, the range of age was (40 - 80) years while the range of age was (60 - 80) years in Vietnam study and the mean age of our population is less than Vietnam population.

The mean serum uric acid level and the percentage of asymptomatic hyperuricemia were higher in the knee osteoarthritis compared to the non - knee osteoarthritis group ( $5.98 \pm 1.34$  mg/dl and  $4.99 \pm 1.05$  mg/dl) respectively, this result is comparable with Cao et al (4) study who found that the mean serum uric acid level among patients with knee osteoarthritis was higher than among patients without knee osteoarthritis ( $6.3 \pm 1.74$  mg/dl vs.  $5.71 \pm 1.45$  mg/dl,  $p = 0.017$ ).

A study conducted in Saudi Arabia, there was positive correlation between the presence of OA in the knee joint and serum uric acid levels (28). This could be explained by increased serum uric acid's pro - inflammatory action (29). The endogenous hormonal environment and genetic predisposition are two additional potential explanations for the correlation between elevated serum uric acid levels and knee OA (30) (31).

There are numerous cohort and population studies have shown links between OA and hyperuricemia, suggesting that hyperuricemia may play a role in this correlation (32) (33) (34). Furthermore, some smaller studies have examined hyperuricemia per se and found a potential link between serum uric acid and the occurrence or progression of OA (35) (3).

Also Using data from the Third National Health and Nutrition Examination Survey (NHANES III) dataset, Wang et al (3) examined older persons and discovered that asymptomatic hyperuricemia raised the chance of knee osteoarthritis by 69% of the population of older adults in the US after accounting for risk variables such as age, race, sex, and educational attainment. The relationship between asymptomatic hyperuricemia and knee osteoarthritis may be caused by a shared pathogenic mechanism between asymptomatic hyperuricemia and knee osteoarthritis.

An in vitro study by Chhana et al (36) demonstrated that elevated serum uric acid levels cause urate crystals to form in the joints, which results in articular cartilage degradation and articular chondrocyte dysfunction that is comparable to endogenous inflammatory processes. Consistent with the in vitro results, the current study indicates a correlation between these two conditions among patients.

A study by Abdurrahman and Rasool (2) conducted at outpatient clinic in Duhok center for rheumatologic diseases revealed a significant positive association between serum uric acid levels and knee joint osteoarthritis.

A study by Reyhan et al (37) which was done in Turkey revealed that Asymptomatic hyperuricemia was found 1 in 5 of advanced - stage knee OA patients and may contribute to inflammation in knee OA.

In this study (64.8%) of the patients were women which is compatible with that found by the Ulm Osteoarthritis study (38) . Even while more women than men seek medical treatment for osteoarthritis in outpatient clinics in our society, the increase in osteoarthritis among postmenopausal women may point to a hormonal etiology of asymptomatic hyperuricemia in knee osteoarthritis. (39).

This study revealed a significant difference ( $p < 0.001$ ) according to education level between individuals with knee osteoarthritis and those without knee osteoarthritis groups, also the same association was found in Lee et al (40) study revealed that lower education level is most strongly relates to higher prevalence of knee OA and knee symptoms.

This study revealed that Diabetes mellitus and hypertension are significantly associated with knee osteoarthritis ( $p < 0.001$ ), this association is compatible with a study done in Babylon City which consisted of 65 individuals (18.4%) of them were diabetics and (64.6%) were hypertensive (41).

Also another study was conducted in Mosul City which revealed positive relationship between diabetes mellitus type 2 and osteoarthritis of the knee joint, however Type 2 diabetes predicts the development of severe knee OA independent of age and other known risk factors for OA (42).

In our study we found smoking is significantly associated with knee osteoarthritis ( $p < 0.001$ ) but other studies revealed no association was detected between smoking and knee osteoarthritis (43) (44).

Yingliang Wei, MD et al (45) showed a positive relationship between climbing stairs and knee osteoarthritis which is in agreement the results in our study.

Ischemic heart disease is significantly associated with knee osteoarthritis ( $P < 0.003$ ) which is consistent with Park et al (46) who found that knee OA may be associated with an increased risk of CVD in a nationally representative population - based context.

Kim et al (1) and Cao et al (4) found that mean serum uric acid levels were significantly higher among women with knee osteoarthritis compared to women without knee osteoarthritis, but there were no significant differences between the two groups among men.

When differentiating patients according to sex, this study revealed a significant association between asymptomatic hyperuricemia and knee osteoarthritis among both sexes.

Wang et al (3) and Cao et al (4) found an association between asymptomatic hyperuricemia and knee osteoarthritis among underweight normal - weight individuals but not among overweight - obese individuals.

Also this study revealed an association between asymptomatic hyperuricemia and knee osteoarthritis in over - weight and obese individuals but to a lesser extent in normal weight individuals. After modification of related factors, such as age, sex a significant association was



identified between asymptomatic hyperuricemia and knee osteoarthritis among normal - weight persons. Normal - weight individuals with asymptomatic hyperuricemia had a higher probability to be diagnosed with knee osteoarthritis.

These findings among the population in this study suggest that, sex and BMI may work as confounding variables that affect the relationship between asymptomatic hyperuricemia and knee osteoarthritis.

This study's strength include focusing on the effects of asymptomatic hyperuricemia on knee osteoarthritis, excluding participants with gout diagnosis, using approved standards to specify asymptomatic hyperuricemia in knee osteoarthritis and makes an effort to account for different risk factors that may possibly complicate the relationship between knee osteoarthritis and asymptomatic hyperuricemia.

A potential limitation in this study could be the inclusion of patients with pre - gout who might have unnoticed symptoms or indicators due to urate crystal precipitation. It is well known that imaging methods like dual - energy CT (DECT) and ultrasound may be useful for evaluating pre - clinical gouty conditions, future research on this topic should be more precisely characterize asymptomatic hyperuricemia (47) (48). Furthermore, the cross - sectional analytic study we used is insufficient to resolve the causality issue.

## 5. Conclusions

Older outpatients with knee osteoarthritis frequently have asymptomatic hyperuricemia as a comorbidity. Once confounding variables such as age, sex, and BMI were taken into account, an independent correlation between asymptomatic hyperuricemia and knee osteoarthritis.

It also found that sex and BMI may be confounding factors that affect the relationship between these two conditions. Since, asymptomatic hyperuricemia and knee osteoarthritis are prevalent in older persons, particularly in the outpatient setting, the findings of this study should be taken into account during clinical practice.

### Conflict of interest

The authors declare no conflict of interest

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