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Association between asymptomatic hyperuricemia and knee osteoarthritis in older outpatients

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Abstract. – OBJECTIVE: To investigate the association between asymptomatic hyperuricemia and knee osteoarthritis in older outpatients in Vietnam.

PATIENTS AND METHODS: This cross-sectional study included 257 older outpatients (195 in the knee osteoarthritis group and 62 in the non-knee osteoarthritis group) aged ≥60 years (mean age 73.31 ± 7.96 years) attending rheumatologic and geriatric clinics from November 2020 to May 2021. Data were collected for both groups, including demographics, symptoms and signs of knee osteoarthritis, serum uric acid levels, and knee radiographs. The association between asymptomatic hyperuricemia and knee osteoarthritis was assessed using logistic regression.

RESULTS: The mean serum uric acid level among patients with knee osteoarthritis was higher than that among patients without knee osteoarthritis (6.3 ± 1.74 mg/dl *vs.* 5.71 ± 1.45 mg/dl, $p = 0.017$). Hyperuricemia was more common among older outpatients with knee osteoarthritis than among those without knee osteoarthritis (39% *vs.* 19%, $p = 0.005$). After adjusting for age, sex, body mass index (BMI), and other comorbidities, the association between asymptomatic hyperuricemia and knee osteoarthritis remained significant (odds ratio [OR] 2.61, 95% confidence interval [CI] 1.22-5.60, $p = 0.013$). Subgroup analyses were performed according to sex and BMI groups. Significant associations between asymptomatic hyperuricemia and knee osteoarthritis were observed among women ($p = 0.017$) and among individuals who were underweight-normal-weight according to BMI ($p = 0.009$).

CONCLUSIONS: Asymptomatic hyperuricemia is a common comorbidity among older outpatients with knee osteoarthritis. An independent association was identified between asymptomatic hyperuricemia and knee osteoarthritis among older Vietnamese outpatients, although sex and BMI may be confounding factors that impact this association.

Key Words:
Knee Osteoarthritis, Asymptomatic hyperuricemia, Older adults, Outpatients.

Introduction

Knee osteoarthritis is one of the most common chronic diseases diagnosed among older adults, causing functional impairment, severely affecting quality of life, and sometimes leading to disability[1]. Asymptomatic hyperuricemia is a common metabolic disorder diagnosed among older adults[2], and some studies have shown that asymptomatic hyperuricemia is common among patients with knee osteoarthritis[3]. 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[4].

As the population of older adults increases, the numbers of older adults diagnosed with knee osteoarthritis and asymptomatic hyperuricemia have also increased. Therefore, the early diagnosis and optimal management of these two conditions have become increasingly important. Although some studies have documented an association between asymptomatic hyperuricemia and knee osteoarthritis among the general population[5], data among older adults are limited.

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To the best of our knowledge, no study has investigated the association between asymptomatic hyperuricemia and knee osteoarthritis among older outpatients despite the frequency at which both conditions are diagnosed within this population. Therefore, the present study was conducted to identify the association between asymptomatic hyperuricemia and knee osteoarthritis among older Vietnamese outpatients.

Patients and Methods

Participants and Setting

This cross-sectional study was conducted among outpatients aged ≥60 years attending geriatric and rheumatologic clinics from November 2020 to May 2021. Exclusion criteria were previous knee injury or knee surgery, gout, rheumatoid arthritis, chronic kidney disease, medications known to cause hyperuricemia (diuretics, cyclosporin, pyrazinamide, ethambutol, aspirin) used during the past two weeks, and serious mental conditions. All participants provided written informed consent. This study was approved by the Ethics Committee of the University of Medicine and Pharmacy at Ho Chi Minh City, Vietnam (reference number: 438/ HĐĐĐ-ĐHYD on July 14, 2020).

Assessment

On the day of the clinic visit, each participant was interviewed to collect demographic information (age, sex, level of education, place of residence, occupational activities, and comorbidities) and knee osteoarthritis symptoms (knee pain and morning stiffness), and signs of knee osteoarthritis (pain, limitation of motion, bone hypertrophy) were examined. Data regarding serum uric acid levels and X-rays of the knee joints (Figure 1) were obtained from the medical records.

Knee osteoarthritis was diagnosed according to the clinical and radiographic criteria established by the American College of Rheumatology in 1986[6]. Patients were defined as having knee osteoarthritis if they described knee pain, osteophytes were visible on X-ray imaging (Figure 1), and at least one of the following criteria was also present: age >50 years, morning stiffness <30 minutes, and crepitus.

Serum uric acid levels were measured quantitatively using an AU5800 machine at the Laboratory Department, University Medical Center (Ho Chi Minh City, Vietnam) and were reported in mg/dl. Asymptomatic hyperuricemia was defined as serum uric acid levels ≥6.8 mg/dl with no prior gout flares or subcutaneous tophi[7].

BMI was calculated as the ratio between body weight (kg) and body height (m^2). Body weight and height were measured using standardized

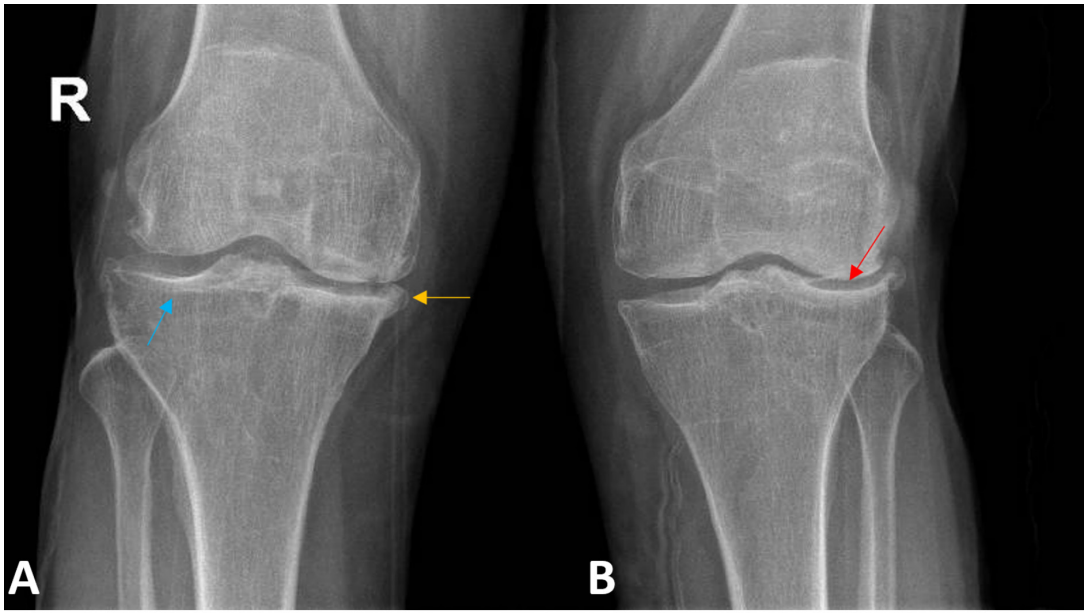

Figure 1. Radiological parameters of Knee Osteoarthritis. **A**, Right knee shows an osteophyte *(yellow arrow)* and blue arrow, subchondral sclerosis *(blue arrow)*. **B**, Joint space narrowing *(red arrow)*.

protocols and identical equipment at both clinics. Patients were stratified into three BMI categories based on the World Health Organization's guidelines for the Asia-Pacific region: underweight (<18.5 kg/m^2), normal weight (18.5-22.9 kg/m^2), overweight-obese (≥23.0 kg/m^2)[8].

Statistical Analysis

All collected data were analyzed using the SPSS Statistics (SPSS Inc., Chicago, IL, USA). Categorical variables are described as the frequency (n) and percentage (%). Continuous variables are described as the mean ± standard deviations. Comparisons between two groups (e.g., group with knee osteoarthritis *vs.* group without knee osteoarthritis) were conducted using the Chi-square test or Fisher's exact test for categorical variables and Student's *t*-test for continuous variables.

Univariate logistic regression was performed on all factors potentially associated with knee osteoarthritis. Variables with *p*-values <0.2 in the univariate analysis were selected for inclusion in the multivariate logistic regression model. All variables were examined for interactions and multicollinearity. The significance level was set at $p < 0.05$.

Results

Of the 257 patients attending the clinics during the study period, 195 patients were diagnosed with knee osteoarthritis, whereas 62 patients had no knee osteoarthritis. Women made up the majority of patients, with three times more women enrolled in the study than men. The mean age was 73.31 ± 7.96 years, and more than one-fourth of patients were very old (≥80 years). According to BMI, the majority of patients were normal weight or overweight-obese, with 45.53% of patients in each category. The proportion of individuals cat-

Table I. Baseline characteristics of participants.

Characteristics	Knee osteoarthritis (n = 195)	Non-knee osteoarthritis (n = 62)	All (n = 257)	*p*-value[a]
Sex, n (%)				
Male	43 (22.05)	23 (37.1)	66 (25.68)	**0.018**[α]
Female	152 (77.95)	39 (62.9)	191 (74.32)	
Age (years)	73.64 ± 8.14	72.26 ± 7.32	73.31 ± 7.96	0.234[*]
Age groups, n (%)				
60-69 years	71 (36.41)	28 (45.16)	99 (38.52)	0.405[α]
70-79 years	70 (35.90)	21 (33.87)	91 (35.41)	
≥80 years	54 (27.69)	13 (20.97)	67 (26.07)	
BMI (kg/m^2)	23.50 ± 3.40	21.87 ± 2.28	23.11 ± 3.24	**0.001**[*]
BMI groupsb, n (%)				
Normal weight	82 (42.05)	35 (56.45)	117 (45.53)	**0.002**[α]
Underweight	13 (6.67)	10 (16.13)	23 (8.95)	
Overweight-obese	100 (51.28)	17 (27.42)	117 (45.53)	
Level of education, n (%)				
Elementary school	72 (36.92)	14 (22.58)	86 (33.46)	0.055[α]
Junior school	58 (29.74)	18 (29.03)	76 (29.57)	
Senior school and above	65 (33.33)	30 (48.39)	95 (36.96)	
Place of residence, n (%)				
Urban	41 (21.03)	16 (25.81)	57 (22.18)	0.430[α]
Rural	154 (78.97)	46 (74.19)	200 (77.82)	
Marital status, n (%)				
Single	4 (2.05)	2 (3.23)	6 (2.33)	0.633[α]
Married	191 (97.95)	60 (96.77)	251 (97.67)	
Occupational activities and comorbidities, n (%)				
Kneeling	62 (31.79)	13 (20.97)	75 (29.18)	0.102[α]
Squatting	63 (32.31)	14 (22.58)	77 (29.96)	0.145[α]
Hypertension	120 (61.54)	32 (51.61)	152 (59.14)	0.166[α]
Diabetes mellitus	62 (31.79)	16 (25.81)	78 (30.35)	0.372[α]

Abbreviations: BMI, body mass index. [a]Knee osteoarthritis group vs. non-knee osteoarthritis group. [b]BMI was classified as underweight (<18.5 kg/m^2), normal weight (18.5-22.9 kg/m^2), overweight-obese (≥23.0 kg/m^2). [*]Normal distribution, *t*-test [α]Chi-square test.

Table II. Serum uric acid levels and asymptomatic hyperuricemia in patients with and without knee osteoarthritis.

Characteristics	Knee osteoarthritis (n = 195)	Non-knee osteoarthritis (n = 62)	All (n = 257)	*p*-value[a]
Serum uric acid (mg/dl)	6.30 ± 1.74	5.71 ± 1.45	6.15 ± 1.69	**0.017**[*]
Asymptomatic hyperuricemia				
Yes, n (%)	76 (38.97)	12 (19.35)	88 (34.24)	**0.005**[α]
No, n (%)	119 (61.03)	50 (80.65)	169 (65.76)	

[*]Normal distribution, *t*-test. [α]Chi-square test.

egorized as overweight-obese was higher in the knee osteoarthritis group than in the non-knee osteoarthritis group (51.28% *vs.* 27.42%). No significant differences were identified between groups for other characteristics, including age, level of education, place of residence, marital status, and occupational activities (such as kneeling and squatting). Hypertension and diabetes mellitus were two common comorbidities identified in this study cohort, identified in 59.14% and 30.35% of patients, respectively, with no significant differences observed between the two groups. Table I summarizes the main characteristics of the study participants.

The serum uric acid levels for the knee osteoarthritis group and the non-knee osteoarthritis group were 6.3 ± 1.74 and 5.71 ± 1.45 mg/dL, respectively. The proportion of individuals experiencing asymptomatic hyperuricemia was significantly higher in the knee osteoarthritis group than in the non-knee osteoarthritis group (38.97% *vs.* 19.35%; $p = 0.005$; (Table II).

After adjusting for related factors, a significant association was identified between asymptomatic hyperuricemia and knee osteoarthritis. Asymptomatic hyperuricemia increased the likelihood of knee osteoarthritis by 2.61-fold ($p = 0.013$; Table III).

A subgroup analysis according to sex revealed that serum uric acid levels and the proportion of individuals experiencing asymptomatic hyperuricemia were significantly higher among women in the knee osteoarthritis than among women in the non-knee osteoarthritis group, but these associations were not observed among men (Table IV).

After adjusting for related factors, such as age, BMI, and occupational activities (kneeling and squatting), the study found a significant association between asymptomatic hyperuricemia and knee osteoarthritis among women, with asymptomatic hyperuricemia increasing the likelihood of knee osteoarthritis by 3.62-fold ($p = 0.017$; Table V).

The subgroup analysis according to BMI groups revealed that serum uric acid levels and the pro-

Table III. Multivariable logistic regression analysis with knee osteoarthritis as the outcome variable.

Characteristics	OR	95% CI	*p*-value
Asymptomatic hyperuricemia	2.61	1.22-5.60	0.013
Female	1.90	0.95-3.82	0.071
Age groups			
60-69 years	1		
70-79 years	0.95	0.47-1.95	0.898
≥80 years	1.31	0.54-3.05	0.529
BMI groups			
Normal weight	1		
Underweight	0.54	0.20-1.45	0.221
Overweight-obese	2.20	1.10-4.41	0.026
Level of education			
Elementary school	1		
Junior school	0.59	0.25-1.39	0.231
Senior school and above	0.54	0.23-1.23	0.142
Kneeling	1.59	0.73-3.46	0.238
Squatting	1.23	0.58-2.64	0.589
Hypertension	1.04	0.55-1.94	0.922

OR, odds ratio; CI, confidence interval; BMI, body mass index.

Table IV. Subgroup analysis according to sex examining serum uric acid levels and asymptomatic hyperuricemia incidence in patients with and without knee osteoarthritis.

	Female			Male		
Characteristics	**Knee osteoarthritis (n = 152)**	**Non-knee osteoarthritis (n = 39)**	***p*-value**	**Knee osteoarthritis (n = 43)**	**Non-knee osteoarthritis (n = 23)**	***p*-value**
Serum uric acid level (mg/dl)	6.08 ± 1.63	5.14 ± 1.27	**0.001***	7.07 ± 1.93	6.67 ± 1.24	0.370*
Asymptomatic hyperuricemia						
Yes, n (%)	53 (34.87)	5 (12.82)	**0.008**[α]	23 (53.49)	7 (30.43)	0.073[α]
No, n (%)	99 (65.13)	34 (87.18)		20 (46.51)	16 (69.57)	

*Normal distribution, *t*-test. [α]Chi-square test.

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

	Univariate analysis		Multivariate analysis	
Characteristics	**OR (95% CI)**	***p*-value[a]**	**OR (95% CI)**	***p*-value[a]**
Asymptomatic hyperuricemia	3.64 (1.34-9.86)	**0.011**	3.62 (1.25-10.45)	0.017
Age groups				
60-69 years	1		1	
70-79 years	1.21 (0.53-2.75)	0.652	0.92 (0.39-2.20)	0.859
≥80 years	1.25 (0.52-3.03)	0.62	0.88 (0.33-2.34)	0.792
BMI groups				
Normal weight	1		1	
Underweight	1.06 (0.31-3.67)	0.921	1.12 (0.31-4.07)	0.864
Overweight-obese	2.78 (1.27-6.11)	0.011	2.78 (1.23-6.28)	0.014
Kneeling	1.29 (0.59-2.79)	0.525	1.03 (0.42-2.53)	0.951
Squatting	1.04 (0.49-2.22)	0.923	0.97 (0.41-2.25)	0.937

OR, odds ratio; CI, confidence interval; BMI, body mass index.

Table VI. Subgroup analysis according to BMI examining serum uric acid levels and asymptomatic hyperuricemia incidence in patients with and without knee osteoarthritis.

	Underweight-Normal Weight			Overweight-Obese		
Characteristics	**Knee osteoarthritis (n = 95)**	**Non-knee osteoarthritis (n = 45)**	***p*-value[a]**	**Knee osteoarthritis (n = 100)**	**Non-knee osteoarthritis (n = 17)**	***p*-value[a]**
Serum uric acid (mg/dl)	6.22 ± 1.60	5.63 ± 1.36	**0.036***	6.37 ± 1.88	5.91 ± 1.70	0.347*
Asymptomatic hyperuricemia						
Yes, n (%)	36 (37.89)	5 (11.11)	**0.001**[α]	40 (40.00)	7 (41.18)	0.927[a]
No, n (%)	59 (62.11)	40 (88.89)		60 (60.00)	10 (58.82)	

*Normal distribution, *t*-test. [α]Chi-square test.

portion of individuals experiencing asymptomatic hyperuricemia were significantly higher among individuals who were underweight or normal weight (underweight-normal-weight group) and diagnosed with knee osteoarthritis than among underweight-normal-weight individuals without knee osteoarthritis. However, these associations were not identified among individuals who were classified as overweight-obese (Table VI).

After adjusting for related factors, such as age, sex, and occupational activities (kneeling and squatting), a significant association was identified between asymptomatic hyperuricemia and knee osteoarthritis among underweight-normal-weight

Table VII. Logistic regression analysis with knee osteoarthritis as the outcome variable in the underweight-normal BMI group.

	Univariate analysis		Multivariate analysis	
Characteristics	**OR (95% CI)**	***p*-value[a]**	**OR (95% CI)**	***p*-value[a]**
Asymptomatic hyperuricemia	4.88 (1.76-13.51)	**0.002**	4.28 (1.45-12.70)	**0.009**
Age groups				
60-69 years	1		1	
70-79 years	1.09 (0.48-2.46)	0.837	0.83 (0.34-2.02)	0.681
≥80 years	2.59 (0.98-6.86)	0.057	1.69 (0.58-4.93)	0.335
Female	2.01 (0.93-4.34)	0.074	2.19 (0.92-5.20)	0.076
Kneeling	3.62 (1.46-8.94)	**0.005**	2.68 (1.00-7.17)	**0.050**
Squatting	1.39 (0.60-3.19)	0.438	1.24 (0.48-3.17)	0.657

OR, odds ratio; CI, confidence interval.

individuals. Underweight-normal-weight individuals with asymptomatic hyperuricemia had a 4.28-fold increase in the likelihood of being diagnosed with knee osteoarthritis ($p = 0.009$; Table VII).

Discussion

To the best of our knowledge, this study is the first to examine the association between asymptomatic hyperuricemia and knee osteoarthritis among adults older than 60 years attending outpatient clinics. The mean serum uric acid level and the proportion of asymptomatic hyperuricemia were both higher in the knee osteoarthritis group than in the non-knee osteoarthritis group, which is consistent with several small studies[9,10]. After controlling for potential risk factors associated with knee osteoarthritis such as age, sex, BMI, level of education, kneeling, squatting, and hypertension[11-13], the present study identified a significant association between asymptomatic hyperuricemia and knee osteoarthritis (OR 2.61, 95% CI 1.22-5.60, $p = 0.017$). Wang et al[5] studied older adults using The Third National Health and Nutrition Examination Survey (NHANES III) dataset and found that asymptomatic hyperuricemia increased the risk of knee osteoarthritis by 69% among the older adult population in the US after adjusting for risk factors, including age, sex, race, and level of education. The association between asymptomatic hyperuricemia and knee osteoarthritis may be due to a shared pathogenic mechanism between asymptomatic hyperuricemia and knee osteoarthritis. Chhana's et al [14] *in vitro* study showed that high serum uric acid levels lead to the deposition of urate crystals in the joints, causing articular chondrocyte dysfunction and articular cartilage damage, similar to endogenous inflammatory processes. The present study suggests an association between these two conditions among older Vietnamese patients attending clinics, which is consistent with the *in vitro* findings.

However, other studies reported different findings. Ding et al[15] found an association between asymptomatic hyperuricemia and the proportion of osteophytes on knee joint X-rays in women but not in men. Kim et al[16] reported that mean serum uric acid levels were higher among women with knee osteoarthritis than among women without knee osteoarthritis, but no significant difference was reported between the two groups among men. When stratifying patients according to sex, the present study also found a significant association between asymptomatic hyperuricemia and knee osteoarthritis among women but not men. In multivariate models adjusting for BMI, Wang et al[5] observed that the association between asymptomatic hyperuricemia and knee osteoarthritis was attenuated, but in models stratified by obesity status, Wang et al[5] found an association between asymptomatic hyperuricemia and knee osteoarthritis among non-obese older adults but not among obese older adults. The present study also found that asymptomatic hyperuricemia was associated with knee osteoarthritis among underweight-normal-weight individuals but not among those classified as overweight-obese. These findings indicate that sex and BMI may be confounding factors that impact the association between asymptomatic hyperuricemia and knee osteoarthritis among the older population.

Strengths of this study include the exclusion of patients diagnosed with gout, the focus on the impacts of non-gout hyperuricemia on knee osteoarthritis, the use of validated criteria to define asymptomatic hyperuricemia and knee osteoarthritis and attempts to control for various risk factors associated with knee osteoarthritis that might potentially confound the association between asymptomatic hyperuricemia and knee osteoarthritis. This study also had several limitations. Only individuals with clinical symptoms or indicators of gout were excluded because in this investigation, asymptomatic hyperuricemia is defined as a serum uric acid level that is over the upper limit of normal (> 6.8 mg/dL) without any recent gout flares or subcutaneous tophi clinically[7]. The inclusion of patients in the pre-gout condition, who could have undetected symptoms or signs from the precipitation of urate crystals, could result in this, and this could be a research drawback. Asymptomatic hyperuricemia should be more accurately described in future research on the topic since imaging techniques like dual-energy CT and ultrasound may be beneficial for assessing pre-clinical gout state[17,18]. Some data were self-reported, which may have led to inaccuracies. In addition, the question of causality cannot be addressed using the cross-sectional methodology we employed.

Conclusions

Asymptomatic hyperuricemia is a common comorbidity among older outpatients with knee osteoarthritis. After adjusting for confounding factors, including age, sex, and BMI, an independent association was identified between asymptomatic hyperuricemia and knee osteoarthritis among older Vietnamese outpatients, and the study identified sex and BMI as potentially confounding factors that impact the relationship between these two conditions. The result of this study should be taken into consideration in clinical practice because asymptomatic hyperuricemia and knee osteoarthritis are both common among older adults, especially in the outpatient setting.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Ethics Approval

This study was approved by the Ethics Committee of the University of Medicine and Pharmacy at Ho Chi Minh City, Vietnam (reference number: 438/ HĐĐĐ-ĐHYD on July 14, 2020).

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are not publicly available due to privacy concerns but are available from the corresponding author on reasonable request.

Authors' Contributions

T.-N. CAO and M.-D. NGUYEN contributed equally to this article as first authorship. T.-N. CAO and M.-D. NGUYEN gave a substantial contribution in acquisition, analysis, and data interpretation. T.-N. CAO and M.-D. NGUYEN prepared, drafted, and revised manuscript critically for important intellectual content. Each author gave the final approval of the version to be published and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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