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URIC ACID CORRELATION WITH SYMPTOMATOLOGY AND IMAGING FEATURES INTENSITY OF KNEE OSTEOARTHRITIS IN JORDANIAN PARTICIPANTS

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Abstract

Background: Knee osteoarthritis occupies the eleventh most participant of worldwide disability. Twenty % of persons of 45 years' age or more experience knee osteoarthritis. The risk of having clinical knee osteoarthritis is 45% (40% in men and 47% in women), with increased risk (60.5%) in obese individuals. Uric acid might participate in the production of osteoarthritis.

Objective: To assess the correlation between uric acid and symptomatology with imaging features intensity of knee osteoarthritis in Jordanian subjects.

Methods: This prospective and observational investigation included 211 subjects, of both sexes and with medial knee osteoarthritis, at Jordanian rehabilitation center, King Hussein medical center, Amman, JORDAN, during the period Sep.2021-Feb.2022, to determine the correlation between uric acid and symptomatology features intensity in terms of Western Ontario and McMaster osteoarthritis Index (pain, stiffness, function and total scores) and with imaging features intensity according to Kellgren-Lawrence scores. Subjects were divided into two groups: Group A with uric acid less than 7 mg/dl [n=155] and group B with uric acid more than 7 mg/dl [n=56].

Student's t test was used for continuous variables and Chi-square with Mann-Whitney tests were used for categorical variables.

Results: There were 145 women and 66 men with knee osteoarthritis. One hundred and fifteen women had uric acid less than 7 mg/dl and 30 women had uric acid more than 7 mg/dl. Forty men had uric acid less than 7 mg/dl and 26 men had uric acid more than 7 mg/dl.

Pain, stiffness, function and total scores were remarkably more in increased uric acid group than in reduced uric acid group (P = 0.003, P = 0.018, P =0.017, P = 0.007, respectively). Increased uric acid group experienced more Kellgren-Lawrence score IV (P = 0.000) than reduced uric acid group.

Women with knee osteoarthritis in increased uric acid group experienced remarkably more pain, stiffness, function and total WOMAC scores than in reduced uric acid group (P = 0.002, P = 0.014, P = 0.007, P = 0.003, respectively), more Kellgren-Lawrence score IV (P = 0.002) than in reduced uric acid group. Female gender, period of knee osteoarthritis and uric acid were correlated with Kellgren- Lawrence intensity. For women with knee osteoarthritis, Kellgren-Lawrence intensity was correlated with period of knee osteoarthritis and uric acid.

Conclusion: Increased uric acid was correlated with increased symptomatology features intensity and increased imaging Kellgren-Lawrence scores in subjects with knee osteoarthritis. Uric acid was remarkably correlated with knee osteoarthritis intensity in women, but not in men.

Introduction

Osteoarthritis induces long standing pain with disturbed movement in old aged individuals (1). Knee osteoarthritis occupies the eleventh most participant of worldwide disability (2). Twenty percent of persons of 45 years' age or more experience knee osteoarthritis (3). The risk of having clinical knee osteoarthritis is 45% (40% in men and 47% in women), with increased risk (60.5%) in obese individuals (4).

Knee osteoarthritis is caused by the destruction of articular cartilage by mechanical loading and long standing inflammation (5). Knee osteoarthritis is a slowly developing disorder, although some subjects experienced a fast developing structural destruction.

Uric acid is an active metabolical molecule. Urate present in joints and soft tissues might cause acute painful gouty arthritis. Uric acid could lead to reduced long standing inflammatory condition despite no gout (6). Aged persons and obesity are frequent risk factors for osteoarthritis and urate presence in tissues. Osteoarthritis and urates attack joints of which is the knee.

Osteoarthritis is correlated with interleukin-1 reaction, mediator of the inflammatory reaction to urate presence in tissues (7). Uric acid might participate in the osteoarthritis. Osteoarthritis intensity was associated with uric acid in subjects without gout (1). Uric acid was not remarkably correlated with knee osteoarthritis but with a correlation between women and knee osteoarthritis (8).

The goal of our investigation was to assess the correlation between uric acid and symptomatology with imaging features intensity of knee osteoarthritis.

Methods

Our prospective and observational investigation included 211 subjects, of both sexes, with body mass index less than 25 kg/m2 , with medial knee osteoarthritis confirmed by the American College of Rheumatology radiological and clinical criteria for diagnosis of knee osteoarthritis(9) at Jordanian Rehabilitation center, KHMC, Amman, JORDAN, during the period Sep.2021-Feb.2022, after obtaining written informed consent from all participants and approval from our local ethical and research board review committee of the Jordanian Royal medical services, to determine the correlation between uric acid and symptomatology features intensity in terms of WOMAC scores(pain, stiffness, function and total score) and with imaging features intensity according to Kellgren-Lawrence scores. Subjects with gouty knee osteoarthritis, knee surgery or on uric acid reducing drugs during the previous 6 months were ruled out.

Western Ontario and McMaster osteoarthritis Index (WOMAC) was used (10). It includes 24 items divided into 3 sub scales: Pain (5 items): during walking, using stairs, in bed, sitting or lying and standing upright; Stiffness (2 items): after first waking and later in the day; Physical Function (17 items): using stairs, rising from sitting, standing, bending, walking, getting in / out of a car, shopping, putting on / taking off socks, rising from bed, lying in bed, getting in / out of bath, sitting, getting on/ off toilet, heavy domestic duties, light domestic duties. Subjects were divided into two groups: Group A with uric acid less than 7 mg/dl(n=155) and group B with uric acid more than 7 mg/dl(n=56). 145 women and 66 men had knee osteoarthritis. One hundred and fifteen women had uric acid less than 7 mg/dl and 30 women had uric acid more than 7 mg/dl. Forty men had uric acid less than 7 mg/dl and 26 men had uric acid more than 7 mg/dl.

45° postero-anterior flexion plain x-ray of both knee joints was done. The knee osteoarthritis severity and osteophytes scoring was achieved according to Kellgren-Lawrence (11). The minimum JSW was defined as the inter-bone distance in millimeters at the medial tibio-femoral joint space (12). The knee joint with the most Kellgren-Lawrence score was taken as the index knee.

Kellgren and Lawrence classification system has 5 scores; 0 (none): completely no x-ray modifications of osteoarthritis, I (doubtful): doubtful joint space narrowing and possible osteophytic lipping, II (minimal): complete osteophytes and possible joint space narrowing, III (moderate): moderate multiple osteophytes, complete narrowing

of joint space and some sclerosis and possible deformity of bone ends, IV (severe): large osteophytes, significant narrowing of joint space, severe sclerosis and complete deformity of bone ends. Osteoarthritis is present at score II but with minimal intensity. This classification is the radiological definition of osteoarthritis.

Statistics
Student's t test was used for continuous variables and Chi-square with Mann -Whitney tests were used for categorical variables. $P < 0.05$ was considered statistically significant.

Results

The mean uric acid in the knee osteoarthritis subjects was 6.1+/-1.4 mg/dl. The WOMAC pain, stiffness, function and overall scores were remarkably more in knee osteoarthritis subjects in the increased uric acid group vs. in the reduced uric acid group ($P = 0.003$, $P = 0.018$, $P = 0.017$, $P=0.007$, respectively). Table I.

On plain x-ray, increased uric acid group demonstrated more intense modifications than reduced uric acid group. The Kellgren-Lawrence score IV in plain x-ray was more common in the increased uric acid group than in the reduced uric acid group (42.9%, 16.1%, respectively, $P = 0.000$). The osteophytes score IV were more common in the increased uric acid group than in the reduced uric acid group (48.2%, 14.2%, respectively, $P = 0.000$) (Table I). The JSW was remarkably less in the increased uric acid group than in the reduced uric acid group ($P = 0.012$) (Table I).

Women with knee osteoarthritis in the increased uric acid group experienced remarkably more pain, stiffness, function and total WOMAC scores than in the reduced uric acid group ($P = 0.002$, $P = 0.014$, $P = 0.007$, $P=0.003$, respectively). Women with knee osteoarthritis in the increased uric acid group experienced more remarkably and commonly Kellgren-Lawrence score IV (40%, 11.3%, respectively) and osteophytes score IV (56.7%, 10.4%, respectively) ($P = 0.002$, $P = 0.000$, respectively) (Table II). JSW was remarkably less in women with knee osteoarthritis in the increased uric acid group than in the reduced uric acid group ($P = 0.015$) (Table II). There was no remarkable discrepancy regarding the symptomatology or imaging outcome between men with knee osteoarthritis in the increased uric acid group and in the reduced uric acid group (Table III).

Factors with remarkable correlation with the Kellgren-Lawrence score in subjects with knee osteoarthritis are: female gender, period of knee osteoarthritis and uric acid. For women with knee osteoarthritis, there was a remarkable correlation between Kellgren-Lawrence score and period of knee osteoarthritis and uric acid.

Discussion

Our investigation found that knee osteoarthritis in the increased uric acid group experienced remarkably worse WOMAC scores than in the reduced uric acid group. Increased uric acid group experienced more intense radiological modifications, with remarkably more common Kellgren-Lawrence score IV, more common score IV osteophytes and less JSW than reduced uric acid group. There was a remarkable increase in uric acid with x-ray intensity according to Kellgren- Lawrence score (13). The most increased uric acid was correlated with osteophytes in knee osteoarthritis, as in our investigation (14) and with generalized osteoarthritis (15). Knee osteoarthritis incidence and intensity were remarkably increased in subjects with increased uric acid (16).

Uric acid did not associate with knee osteoarthritis intensity using WOMAC pain score, Kellgren-Lawrence score and JSW. 22.7% of the knee osteoarthritis subjects experienced Kellgren- Lawrence score I and not Kellgren-Lawrence score more than II for osteoarthritis in our investigation (17). Knee osteoarthritis subjects with uric acid more than 6.8 mg/dl experienced remarkably less JSW following 2 years than knee osteoarthritis subjects with uric acid less than 6.8 mg/dl (18), attributing uric acid to the development of intensity of the knee osteoarthritis. The association between uric acid and WOMAC score found a remarkable enhancement percentage of overall WOMAC score from 57.9 to 23.5%(19) and from 49 to 39%(20) at 20 weeks in a colchicine group.

We found that women with knee osteoarthritis in increased uric acid group experienced remarkably more intense WOMAC scores, and in plain images, experienced more common Kellgren- Lawrence score IV, more common

score IV osteophytes and less JSW than women in reduced uric acid group. There were no remarkable discrepancies in terms of symptomatology and imaging outcome between men with knee osteoarthritis in increased uric acid group vs. reduced uric acid group. The most increased uric acid was associated with osteophytes in women with knee osteoarthritis, but not in men, as in our investigation (14). The uric acid was associated with knee osteoarthritis and with hand osteoarthritis in women, but not in men (1). Uric acid was not remarkably correlated with osteoarthritis in men with osteoarthritis as with an association in women (8). The sex discrepancies of the correlation between uric acid and knee osteoarthritis intensity are induced by the pathological biomechanical and sex hormone because uric acid increases remarkably following menopause (21).

Female gender, period of knee osteoarthritis and uric acid were correlated with Kellgren- Lawrence score in knee osteoarthritis. For women with knee osteoarthritis, there was a remarkable correlation between Kellgren-Lawrence score and period of knee osteoarthritis and uric acid. There was a correlation between osteophyte intensity and uric acid in women and the incidence of osteophytes was higher in the highest level of uric acid vs. the lowest in women (14) as in our investigation, but not in men.

Synovial fluid is mostly a serum hyper-filtrate. Synovial membrane in osteoarthritis increases urates in the joint as osteoarthritis synovium is permeable to water more than to urates. Resorption of water from the joint space to circulation is faster than urate resorption in the joint causing a relative increase in urate (22). The association between uric acid and osteoarthritis explains that high synovial fluid urate is causative for cartilage insult (1). Chondrocytes reflect urate transporters and are able to take up soluble urate. Urate causes intra-cellular pro-oxidant action and synthesis of interleukin-1β, cytokine responsible in osteoarthritis (18).

Osteoarthritis can be fastened by chondrocytes death by uric acid- dependent cycle (23). Dead chondrocytes might produce uric acid to initiate inflammatory reaction of cells starting osteoarthritis.

Increased uric acid is an element of metabolic syndrome and abdominal obesity is correlated more with knee osteoarthritis and hyperuricemia but not body mass index. Uric acid was remarkably correlated with knee osteoarthritis intensity in women, but not in men. Men could have a different uric acid level. We chose only subjects with medial knee osteoarthritis (medial joint space width (JSW) is less than lateral JSW on plain x-ray), along with the OA Research Society International

recommendations (24). Subjects with body mass index more than 25 kg/m2 were not selected to reduce effect of obesity on OA/inflammatory biomarkers (17).

Conclusion

Increased uric acid is correlated with increased symptomatology features intensity and more increased imaging Kellgren-Lawrence scores outcome in subjects with knee osteoarthritis. Uric acid was remarkably correlated with knee osteoarthritis intensity in women, but not in men

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Table I. Demographics, Symptoms and imaging features in osteoarthritis subjects

	Group A	Group B	P
Uric acid(mg/ml)	less than 7	more than 7	
No (%)	155(73.5)	56(26.5)	
Age (yrs.) (average)SD	58.4(4.6)	58.2(5.6)	0.898
Gender (no, %) **F**	115 (74.2)	30 (53.6)	0.012
M	40(25.8)	26(46.4)	
BMI (kg/m^2) (average)SD	23.8(1.2)	24.0(1.4)	0.452
Period of knee osteoarthritis (yrs.) (average)SD	9.4(2.1)	9.0(2.6)	0.469
WOMAC score			
Pain(average)SD	7.1(4.7)	9.0(5.1)	0.004
Stiffness(average)SD	1.0(2.2)	1.4(2.3)	0.019
	29.6(10.9)	33.8(11.2)	0.018
Function (average)SD	40.0(14.8)	46.6(15.2)	0.008
Overall score(average)SD			
Kellgren-Lawrence score (n, %)			
II	75(48.4)	13(23.2)	
III	55(35.5)	19(33.9)	
IV	25(16.1)	24(42.9)	<0.001
Osteophytes score (n, %)			
II	78(50.3)	11(19.6)	
III	55(35.5)	18(32.1)	
IV	22(14.2)	27(48.2)	<0.001
JSW (mm) (average)SD	1.63(1.35)	0.98(1.38)	0.013

Table II. Demographic, symptoms, and imaging features in women with knee osteoarthritis.

	Group A	Group B	P
Uric acid(mg/dl)	Less than 7	More than 7	
No (%)	115(79.3)	30(20.7)	
Age (yrs.) (average)SD	58.1(4.4)	58.2(5.5)	0.970
BMI (kg/m^2) (average)SD	23.8(1.2)	23.9(1.5)	0.790
Period of knee osteoarthritis (yrs.) (average)SD	9.6(2.0)	9.4(2.6)	0.732
WOMAC score			
Pain (average)SD	7.2(4.6)	9.7(5.1)	0.003
Stiffness (average)SD	0.9(2.1)	1.5(2.4)	0.015
Function (average)SD	29.5(10.9)	35.7(10.7)	0.008
Overall score(average)SD	40.0(14.7)	49.3(14.7)	0.004
Kellgren-Lawrence score (n, %)			
II	62(53.9)	8(26.7)	
III	40(34.8)	10(33.3)	

IV	13(11.3)	12(40)	0.003
Osteophytes score (n, %)			
II	58(50.4)	4(13.3)	
III	45(39.1)	9(30.0)	
IV	12(10.4)	17(56.7)	<0.001
JSW (mm) (average)SD	2.28(1.28)	1.18(1.78)	0.016

Table III. Demographic, symptoms and imaging features in men with knee osteoarthritis.

	Group A-males	**Group B-males**	**P**
Uric acid(mg/dl)	Less than 7	More than 7	
No.(%)	40(60.6)	26(39.4)	
Age(yrs.)average(SD)	59.0(5.3)	58.3(5.9)	0.703
BMI (kg/m^2) (average)SD	23.9(1.4)	24.2(1.4)	0.512
Period of knee osteoarthritis (yrs.)(average)SD	8.8(2.4)	8.6(2.6)	0.787
WOMAC score			
Pain(average)SD	6.9(5.0)	8.2(5.1)	0.242
Stiffness(average)SD	1.1(2.3)	1.3(2.2)	0.542
Function (average)SD	29.6(10.9)	31.6(11.6)	0.512
Overall score(average)SD	40.0(15.3)	43.5(15.5)	0.403
Kellgren-Lawrence score(n, %)			
II	13(32.5)	5(19.2)	
III	15(37.5)	9(34.6)	
IV	12(30.0)	12(46.2)	0.452
Osteophytes (n, %)			
II	19(47.5)	7(26.9)	
III	10(25.0)	9(34.6)	
IV	11(27.5)	10(38.5)	0.243
JSW (mm) (average)SD	0.98(0.48)	0.93(1.41)	0.575