Published in final edited form as:

J Clin Rheumatol. 2015 March ; 21(2): 63–71. doi:10.1097/RHU.0000000000000217.

Presence of Gout is Associated With Increased Prevalence and Severity of Knee Osteoarthritis:

Among Older Men: Results of a Pilot Study

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Abstract

Background—Gout and osteoarthritis (OA) are the most prevalent arthritides, but their relationship is neither well established nor well understood.

Objectives—We assessed whether a diagnosis of gout or asymptomatic hyperuricemia (AH) is associated with increased prevalence/severity of knee OA.

Methods—119 male patients ages 55–85 were sequentially enrolled from the primary care clinics of an urban VA hospital, assessed and categorized into 3 groups: gout (ACR Classification Criteria), AH ([serum urate] ≥ 6.8 mg/dL, no gout), and control ([serum urate] < 6.8 mg/dL, no gout). 25 patients from each group subsequently underwent formal assessment of knee OA presence and severity (ACR Clinical/Radiographic Criteria, Kellgren-Lawrence (KL) grade). Musculoskeletal ultrasound was used to detect monosodium urate (MSU) deposition at the knees and 1st metatarsophalangeal (MTP) joints.

Results—68.0% of gout, 52.0% of AH, and 28.0% of age-matched control subjects had knee OA (gout vs. control, $P=0.017$). Odds ratio for knee OA in gout vs. controls was 5.46 prior to, and 3.80 after adjusting for BMI. Gout subjects also had higher KL grades than controls ($P=0.001$).

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None of the authors report any conflicts of interest regarding this study.

Subjects with sonographically-detected MSU crystal deposition on cartilage were more likely to have OA than those without (60.0 vs 27.5%, $P=0.037$), with crystal deposition at the 1st MTP joints correlating most closely with OA knee involvement.

Conclusion—Knee OA was more prevalent in gout patients vs. controls, and intermediate in AH. Knee OA was more severe in gout patients vs. controls.

INDEXING TERMS

Gout; Hyperuricemia; Knee Osteoarthritis; Biomarker; Musculoskeletal Ultrasound

INTRODUCTION

Osteoarthritis (OA) is the most prevalent joint disease, affecting over 20 million Americans (1). OA causes pain, disability and economic burden (2). Whereas OA is initiated by mechanical stress on cartilage, its progression depends on cellular and biochemical factors, including chondrocyte activation and the secretion of inflammatory mediators (3). Molecules implicated in OA pathogenesis include cytokines such as IL-1 β , which stimulates metalloproteinase production and adversely affects chondrocyte survival (4–6). At present, no reliable biochemical markers serve as risk factors for, or predict clinical OA progression, though multiple potential markers are under study (7, 8). Treatment is primarily aimed at alleviating symptoms; current management is suboptimal, and disease-modifying medications are lacking. There is thus a need to identify severity and progression markers, as well as remediable risk factors that may serve as OA pharmacologic targets.

Gout is the most common inflammatory arthritis, affecting 3–12 million Americans (1), and recent epidemiologic evidence suggests that the global burden of gout is rising (9). Clinicians have sometimes affirmed that OA and gout occur in association, but few studies have examined this potential relationship (10, 11). Elevation of serum uric acid (sUA) is the primary risk factor for gout (12). At high concentrations sUA can crystallize as monosodium urate (MSU), stimulating the NLRP3 inflammasome and promoting IL-1 β production (13, 14). The result is acute and sometimes chronic inflammation. MSU crystal aggregates (tophi) can also directly disrupt cartilage. Conceivably these, or other yet-undefined mechanisms, could promote OA (15, 16).

Soluble urate is biologically active and may have inflammatory effects, independent of those related to MSU crystals (17–20). A limited number of studies suggest a possible association between hyperuricemia and OA (21, 22), but these findings await validation. Moreover, hyperuricemia in the absence of gout does not unequivocally imply an absence of MSU crystals, since some patients with asymptomatic hyperuricemia (AH) may harbor MSU aggregates on or within their cartilage, tendons and/or synovium (23, 24). Thus a link between AH and OA, even in the absence of gout, might be driven through crystalline MSU. This possibility can be addressed by using musculoskeletal ultrasound (MSK-US) to identify either tophi or urate crystal deposition on cartilage, the latter defined by the so-called double contour sign (readily distinguished from chondrocalcinosis by location at the articular surface rather than within the articular cartilage) (25–27). The presence of hyperuricemia might also provide a background against which pericellular increases in urate, such as occur

during chondrocyte cell death, could promote the local formation of crystals at the microscopic level (15). Thus, even in the absence of frank gout, elevated sUA levels in AH might have adverse effects on cartilage. To address the interaction between sUA, gout, and OA, we assessed whether the presence of gout or AH predicts increased prevalence and/or severity of knee OA, compared with non-gout, non-hyperuricemic controls.

METHODS

Our protocol was approved by the Institutional Review Boards of the New York Harbor Healthcare System of the Department of Veterans Affairs (VA) and New York University School of Medicine. A VA setting was selected to facilitate enrollment of an older male population, with high penetrance of both gout and OA. The study consisted of two visits per subject. At visit 1, sUA level and diagnostic groups were determined. At visit 2, knee OA presence and characteristics were assessed, as well as presence of crystals on cartilage. The primary outcomes were tibiofemoral knee OA presence, based on American College of Rheumatology (ACR) Clinical/Radiographic Criteria (28) (which require the simultaneous presence of pre-specified clinical as well as X-ray findings), and radiographic knee OA severity measured by Kellgren-Lawrence (KL) grading (29). Secondary outcomes included knee OA based on ACR Clinical Criteria (no X-ray findings required), and frequency of bilateral knee OA, RAPID3 (30) and Western Ontario and McMaster Universities osteoarthritis index (WOMAC) (31) scores as indicators of OA severity. Compared with ACR Clinical/Radiographic Criteria (sensitivity 91%, specificity 86%), ACR Clinical Criteria rely more on physical examination, do not include radiographic findings, and are slightly more sensitive (95%) but less specific (68%) for diagnosing knee OA(28).

Visit 1

Screening and enrollment of study participants were conducted during routine visits to the primary care clinics of the VA New York Harbor Health Care System, New York Campus. Prior to clinic sessions, electronic medical records of scheduled subjects were prescreened, and during the clinic sessions participating primary care physicians offered all potentially eligible patients the opportunity to participate in the study. Inclusion criteria were male sex and age 55–85 years. Exclusion criteria included current or prior history of non-gouty inflammatory arthritis, known chondrocalcinosis of any knee, inflammatory bowel disease, cutaneous psoriasis, hemochromatosis, hemodialysis, total knee replacement and history of severe knee trauma. Eligibility of subjects who agreed to participate was confirmed by investigator interview immediately after their primary care visits. Both prescreening and visit assessments were conducted by Dr. Rennie Howard, lead investigator. Subjects then underwent gout assessment (1977 ACR preliminary criteria for the classification of gout (32), as well as number and location of prior gout attacks) and sUA level testing. Enrolled subjects were subsequently assigned to: Group 1, control subjects (no prior or current gout, sUA < 6.8 mg/dL); Group 2, subjects with AH (no prior gout or current gout, sUA ≥ 6.8 mg/dL); or Group 3, subjects with gout (regardless of current treatment or sUA value). Subjects were specifically not queried about a historical diagnosis of knee OA at any time during the study.

Visit 2

Subjects from each group were sequentially invited to return for assessment for knee OA, until 25 subjects in each group completed the second visit. Sample size was determined based on power analysis. Visit 2 included collection of additional demographic data, including race, ethnicity and history of joint use potentially contributing to knee OA. Subjects were queried about knee pain and stiffness (present/absent), and duration of knee morning stiffness (or < 30 minutes). Each subject completed the RAPID3 and WOMAC instruments. A rheumatologist blinded to groups (JS) examined each subject for physical evidence of knee OA according to ACR criteria, using a standardized examination protocol. Subjects were also assessed for tophi (ear helices, olecranon bursae, hands, knees and feet).

Imaging

A single-view posteroanterior weight-bearing radiograph of bilateral knees was obtained for each subject, using the SynaFlex® positioning frame (X-ray beam angle = 10° for all subjects). Radiographs were read by a musculoskeletal radiologist (SG) blinded to subject group; assessment included KL score and chondrocalcinosis determination for each knee. MSU crystal deposition was assessed by performing MSK-US on the knees (transverse suprapatellar view of the femoral articular cartilage in maximal flexion) and first metatarsophalangeal (MTP) joints (longitudinal dorsal and medial views) (RH), using a frequency of 12 MHz for the knees and 18 MHz for the MTPs (MyLab25, Biosound Esaote, Indianapolis Indiana). MSK-US images were read independently by two rheumatologists blinded to subject and subject group (RH, JS); concordance between readers was high (kappa 0.94–1.00) (33). Presence/absence of MSU crystals on MSK-US (double-contour sign on knee cartilage, tophaceous deposition on MTP joint) was analyzed for correlation with the three subject groups, and with sites of OA localization.

Power analysis

Assuming a 30% prevalence of OA in adult men older than 60 years of age (1), a hypothesized increase in OA prevalence associated with either hyperuricemia or gout was estimated based upon previously published data (11) in which the increased odds of OA associated with gout ranged from 3 (knee OA) to 8 (OA in any site). For the sample size selected, global test of difference in proportions between the control, AH and gout groups would have 83% power to detect an associated increase in prevalence from 30% to 75% (odds ratio of 7) in the gout group and a more moderate increase to 60% in AH (odds ratio of 3.5). Assuming AH had either no association with OA or the same effect as gout, the power to detect differences between groups using the global test increased to 93%. Sample size was estimated using nQuery Advisor 7.0 (Saugus, MA).

Knee activity score

History of joint use potentially contributing to knee OA (Knee Activity Score) was determined by questionnaire, based on prior studies examining the role of physical activity in OA (34–36). Subjects were asked whether the following activities were required on a daily basis, during the subject's longest occupation or military service: standing > 2 hours/day, squatting > 30 min/day, kneeling > 30 min/day, climbing stairs > 10 flights/day, lifting

weights > 12 pounds/day, walking > 2 miles/day). One point was assigned to each activity for a maximal possible score of 6.

Statistical Analysis

Summary statistics for demographic, clinical features and self-reported outcomes as well as prevalence of OA were estimated by disease group, as well as by flare location (self report) within the gout group. Global tests of differences in demographic, clinical features and outcomes between groups were estimated using the Kruskal-Wallis test for continuous measures and Chi-square test for prevalence and categorical measures (Fisher's Exact was used when assumptions for Chi-square test were not met). Post-hoc pairwise group analysis of any global significant differences was examined using a Bonferonni-corrected test; the critical value for all pairwise comparisons is $p=0.017$. Nonparametric methods were utilized due to the small sample size within each group. Unadjusted odds for knee OA prevalence were estimated using logistic regression, allowing for group differences to be estimated by linear contrast from the overall regression model. Multivariable logistic regression was also used to provide odds for knee OA prevalence, adjusting for possible confounders or observed differences in demographic or clinical features. Statistical analysis was completed using Stata 11.2 (College Station, TX).

RESULTS

Subject Characteristics

129 subjects were screened, and 119 enrolled during visit 1 (3 subjects were excluded during screening, and 7 declined to participate) (Figure 1). 4 subjects failed to obtain sUA assessment and also were excluded. Among the remaining 115, the frequency of control, AH and gout diagnoses were 47.8% (55/115), 27.0% (31/115) and 25.2% (29/115), respectively. Subjects were contacted for second visits in the order in which they were initially screened, regardless of diagnosis, until each group reached 25 in number. 24 subjects could not be reached to establish appointments, and 8 declined to participate further. We reached the target number of subjects in the control group before the other two groups; 8 control subjects were therefore excluded from visit 2 to prevent over-enrollment.

For the 25 subjects in each group who completed visit 2, demographics, comorbidities and medication use are summarized in Table 1. Age and race were similar across the groups. Moreover, the variance of age between groups was estimated and found to not be statistically different (not shown). The gout group completed fewer years of formal education, had increased body mass index (BMI), and tended to report less current smoking ($p=0.067$) vs. the control group. No other statistically significant pairwise comparisons were detected for formal education, smoking or BMI (not shown). eGFR was significantly lower in the gout group vs. control or AH (gout vs. control, $p=0.002$; gout vs. AH, $p=0.004$). Prevalence of cardiovascular disease, hypertension and diuretic use were lowest in the control group, but these differences were not statistically significant. Outpatient clinic usage was similar among all groups. Knee Activity Score did not differ between the groups. sUA levels were lower in the control group than in the AH and gout groups, and colchicine and urate-lowering therapy use were seen only in the gout group, consistent with the study

design and the indications for gout treatment. Among the gout group, no patient had an attack of gout, by either self-report or joint examination, at the time of either study visit.

Knee OA prevalence

Prevalence of knee OA differed among the three groups (Figure 2A). Applying ACR Clinical/Radiographic Criteria (primary outcome), knee OA prevalence was highest in the gout group (68%), intermediate in the AH group (52%), and lowest in the controls (28%). The unadjusted odds of knee OA in the gout group were more than 5-fold above those for the control group (Table 2). The unadjusted odds for knee OA in the AH group were nearly 3-fold above those for the control group, but this difference did not achieve statistical significance. We found similar trends using the less stringent ACR Clinical Criteria for OA, with OA again more prevalent in the gout group.

Knee OA severity

Among patients meeting Clinical/Radiographic criteria for OA, subjects in the gout group had higher mean KL grades (primary outcome) overall than those in the control group, indicating greater radiographic OA severity (Table 3). Gout subjects also had higher KL scores for the right knee, and a trend toward higher KL scores for the left knee, compared with controls. Similar results were seen among patients meeting ACR Clinical Criteria for OA. Subjects with AH demonstrated KL scores that were intermediate between the control and gout groups, but these scores did not always achieve statistical significance vs. the control group. Bilateral knee OA was more common in the gout vs. control group (Table 2, 3). Although differences in WOMAC and RAPID3 scores did not achieve statistical significance, subjects in the gout group tended to report more pain, stiffness, functional difficulty, and higher RAPID3 scores than subjects in the other groups (Table 3). Of the maximum WOMAC scores reported, the highest was in the gout group and the lowest was in the control group. Consistent with the established utility of WOMAC and RAPID3 for functional assessment of OA, patients with OA, regardless of group, had higher WOMAC and RAPID3 scores than those without OA (See Table, Supplemental Digital Content 1, WOMAC RAPID3 in patients with vs without AO).

Adjustment for BMI

Prevalence of knee OA between groups, after accounting for possible confounders or other group differences, was investigated using multivariable logistic regression. As noted, the only features differing significantly between groups were education, eGFR and BMI. Neither formal education level nor eGFR were determined to be associated with prevalence of knee OA and are therefore not further reported. Consistent with prior reports (37, 38), logistic regression models estimating odds of OA between groups indicated that unit increase in BMI was associated with increased odds for both ACR clinical/radiographically-defined knee OA, and ACR clinically-defined knee OA, independent of gout/AH status (odds ratio 1.1 (C.I. 0.99, 1.21) for gout, and 1.12 (C.I. 1.01, 1.24) for AH per unit BMI increase, respectively). Nonetheless, differences in the prevalence of clinical/radiographically-defined knee OA, as well as in the prevalence of clinical/radiographically-defined bilateral knee OA, remained significant between the gout and control groups even after BMI adjustment (Table 2). Differences in the prevalence of clinically defined bilateral

knee OA also remained significant between the gout and control groups after adjustment for BMI. Age and diuretic use were also examined as potential covariates, but were not found to be statistically significant in any of the models.

To further understand the relationship between gout, BMI and OA, we stratified subjects into non-obese (BMI<30) and obese (BMI ≥ 30) groups. For the non-obese subjects, BMI did not differ significantly between control, AH and gout subjects (BMI control 25.9±2.7 (n=21); AH 25.5±2.8 (n=13); gout 26.9±2.4 (n=8); one-way ANOVA, P=0.49). Among these non-obese subjects, clinical/radiographically-defined knee OA prevalence was 19% in the control group, 31% in the AH group and 63% in the gout group (gout vs. control, P=0.04; gout vs. AH, P=0.16; AH vs. control, P=0.3) (Figure 2B). These values resulted in an odds ratio for knee OA of 4.6 for the non-obese gout vs. the non-obese control group. In contrast, obese subjects experienced a higher prevalence of knee OA than non-obese patients in all three groups, but smaller differences in knee OA prevalence between the three groups. Nonetheless, gout patients again demonstrated a trend toward more prevalent knee OA (controls 50% (n=8); AH 50% (n=12); gout 69% (n=17); control vs. gout, P=0.1) (Figure 2B). As in the case of the non-obese subjects, for obese subjects BMI did not differ significantly between the control, AH and gout subgroups (BMI control 33.25±0.5; AH 37.37; gout 33.6±2.7; one-way ANOVA P=0.19). These data indicate that gout is an independent risk factor for OA, but that the impact of BMI may obscure the impact of gout on OA among obese populations.

Crystal deposition, gout attack location, and OA

Knee and 1st MTP MSK-US images were available for all subjects (except one with AH). 21 subjects had evidence of MSU crystal deposition (16 gout, 4 AH, 1 control); eight had cartilage surface crystal deposition (double contour sign) within at least one knee (4 gout, 3 AH, 1 control), with the remainder having crystal deposition (tophus) at the 1st MTP joint. When comparing subjects with versus without MSK-US evidence of MSU crystal deposition amongst all subjects with AH or gout, those with crystal findings had significantly higher rates of ACR clinical/radiographic knee OA than those without (Figure 3A). Conversely, patients with knee OA were more likely to show evidence of MSU crystal deposition than those without OA (Figure 3B). Interestingly however, it was specifically the presence of MSK-US-defined MSU deposition in the MTP joints, rather than in the knees themselves, that was associated with a statistically significant increase in knee OA prevalence (Figure 3A,B). By study design, subjects with known history of pseudogout and/or chondrocalcinosis were excluded. However, we did examine the protocol knee X-Rays for chondrocalcinosis and detected calcium deposition in a total of 10 subjects, only 3 of whom also had knee OA. Since there was also no clear relationship between chondrocalcinosis and urate status in these three subjects (two had AH and one had gout), chondrocalcinosis was effectively eliminated as a confounding factor. Among the gout subjects, a history of gout attacks specifically in the knees also did not convey an increased risk of knee OA (Figure 3C).

DISCUSSION

Our data indicate that patients with gout have an increased prevalence of knee OA relative to non-gout controls. Moreover, the presence of gout was associated with more severe structural knee OA, defined as higher KL grades and more bilateral knee OA involvement. Self-reports of joint function (WOMAC index) and overall well-being (RAPID3) also tended to be worse among gout subjects, but structural, functional and symptom severity must be assessed as separate entities. Thus, the presence of gout identifies individuals more likely to have knee OA, more likely to have structurally severe knee OA, and perhaps, more likely to experience worse knee OA pain and dysfunction. Less certain is whether AH is associated with increased risk for knee OA. By most parameters, AH subjects demonstrated prevalence and severity of knee OA that were intermediate between the control and gout groups. However, for many of these measurements the differences between the AH and the control and/or gout groups did not achieve statistical significance, possibly because of our relatively small sample size. Larger studies with greater power will be needed to confirm or refute an increased prevalence of knee OA in individuals with AH.

The association we observed between gout and OA might represent a cause-and-effect relationship, or might result from a common risk factor shared by both diseases. Possible common factors include obesity, older age and history of knee use and/or trauma. (39, 40). However, the association between gout and OA persisted even after accounting for BMI, and particularly among non-obese subjects, suggesting that obesity is insufficient to fully explain the gout/OA association. Furthermore, our gout and control groups had similar mean ages, so age also could not account for the observed differences in OA prevalence. History of strenuous knee activity also did not differ between the groups, and we excluded patients with a history of major knee trauma from the study.

In considering a possible cause-and-effect relationship between gout and OA, it seems unlikely that OA would promote gout, since OA is a local, and gout a systemic disease. Indeed, we found no concordance between the location of OA and the location of specific gouty attacks. However, the number of subjects in this sub-analysis was small, and it remains possible that the presence of OA might in some manner promote the localization of gout attacks to the OA-involved joint, once hyperuricemia had been independently established (41, 42). Consistent with this idea, Simkin et al reported on a series of patients developing gout in Heberden's nodes and suggested that the dystrophic surface may serve as a site for crystal aggregation (43). Alternatively, gout could in some way promote knee OA presence/severity. Consistent with a precedent role for gout in OA, Kawenoki-Minc et al reported that the time from onset of gout to onset of osteoarthritis is typically 8 years (44). Mechanisms that might theoretically participate in such a relationship include effects of gouty attacks and/or macroscopic crystal deposition on knee joint structures. Such a mechanism has been proposed by Roddy et al. (11) who found an association found between joints previously affected by gout and the subsequent presence of OA (applying OA clinical criteria only). In contrast, in our study, we observed that a history of gout attacks in the knees was not more strongly associated with an increased risk of knee OA compared with gout attacks elsewhere. Moreover, although the presence of MSK-US-defined MSU crystal deposition was associated with increased knee OA prevalence, knee OA risk was associated

mainly with crystal deposition in the MTP joints rather than in the OA-affected knee(s) themselves. Together, these data suggest an indirect rather than a direct relationship between gout, crystal deposition and knee OA. Crystal deposition in non-knee joints (e.g., MTP joints) might cause gait abnormalities that indirectly promote knee OA. Alternatively, either gouty attacks or crystal-deposition in OA-unaffected joints could be a marker for systemic inflammation (a variable not assessed in our study) that might in turn promote OA by heretofore unappreciated mechanisms (e.g., effects of systemic cytokines on cartilage). These possibilities are not mutually exclusive. Once again, however, the numbers of subjects included in our subanalyses were small, and further investigation is needed. Indeed, in a prior MSK-US study, the presence of urate deposits on the surface of talar cartilage was directly associated with the presence of degenerative lesions (45).

It is also conceivable that MSU crystallization, either in gout or AH subjects, could be occurring in OA-affected knees at a microscopic level undetectable by MSK-US, and that detectable crystallization elsewhere marks the propensity for such microscopic crystallization to occur. Recently, Denoble et al. proposed that in patients with knee OA, dying chondrocytes locally produce MSU as a “danger signal”, promoting further OA progression via inflammasome-mediated release of IL-1 β (15). Such a process must involve MSU crystallization (since only the crystal form of MSU activates the NLRP3 inflammasome), but only at a microscopic, pericellular level (13, 46). In that context, the elevated serum and synovial fluid UA concentrations seen in gout and/or AH could provide a background against which microenvironmental MSU precipitation could more readily happen. Interestingly, recent studies suggest that colchicine, a standard medication for gout and an inhibitor of inflammasome-driven IL-1 β generation, may be of benefit for OA management (47, 48).

Our study had both strengths and limitations. Strengths include the prospective, face-to face nature of our enrollment process that allowed us to determine, with a high degree of accuracy, whether enrollees had gout, AH or neither, and whether knee OA was present or absent according to formal criteria. For diagnosing gout we relied on ACR clinical criteria which, although in standard use for many years, have not been validated. Despite the stringency of these particular criteria, our ability to query our patients directly about their gout likely ensured that we did not miss gout diagnoses for failure to collect criteria evidence. We did not collect synovial fluid, which might have led us to additional gout diagnoses. In addition, sUA concentrations can fluctuate, and our use of a single sUA measurement may have led us to under-recognize AH in a small percentage of subjects, whose urate levels were transiently low and who were therefore were incorrectly designated as controls. Our focus on older men allowed us to enrich for gout, but our findings may not be generalizable to younger and/or female populations. Our use of standardized X-rays and MSK-US allowed us to define and assess OA severity and crystal deposition according to rigorous criteria. On the other hand, our modest sample size may have limited our ability to assess the impact of AH on OA, or to perform analyses on smaller subsets of patients. Several of the differences we observed that did not achieve significance might well have done so had our sample sizes been larger.

Our assessment of only a single, protocolized anteroposterior X-ray allowed us to remain consistent with validated radiographic grading systems, but may have led us to overlook associations between gout and disease of the patellofemoral knee joint compartment, not visible in the prescribed view. Similarly, our ultrasound focus on two specific aspects of gout (double contour, tophi) may have led us to overlook evidence of urate deposition elsewhere, for example in soft tissue structures or in the synovial fluid itself (“snowstorm sign”). Finally, and most importantly, the nature of our study design did not permit us to ascertain whether current gout or AH predict future OA incidence and/or progression. Larger, prospective studies will be needed to clarify any possible causative role of urate or gouty inflammation, and to assess for more subtle outcome differences between the three subject groups.

In summary, we conclude that the presence of gout, and possibly AH, is associated with increased knee OA prevalence and severity in older men. While direction of the association between gout and OA is still unknown, and may very well be bi-directional (49), if gout and/or AH can be shown to predict future OA progression they may serve as useful prognostic signs in clinical practice, and as biomarkers to help identify high-risk subjects suitable for interventional trials. The possibility that gout and/or AH might be a factor contributing to future OA progression, together with the fact that both AH and gout can be managed using approved urate-lowering therapies, suggests that trials of urate-lowering and/or gout treatment optimization for OA management may deserve future consideration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Yusuf Yazici, MD, NYU School of Medicine, for valuable input regarding study design; Jeffrey Greenberg, MD, MPH, NYU School of Medicine, for advice on trial design and data analysis; Steven Abramson, MD, NYU School of Medicine, for his expertise in OA and OA investigation, and for supporting Dr. Howard during the training period; Ralf Thiele, MD, University of Rochester Medical Center, for his assistance with MSU ultrasound training; and Czeslaw Kowal, PhD, for assistance with translation of a published paper from Polish to English. The authors would also like to thank the following primary care physicians at the New York Harbor Healthcare System VA for referring their patients to the study: Kelly Crotty, MD, Anne Dembitzer, MD, Sabrina Felson, MD, Vivian Hayashi, MD, and Margaret Horlick, MD.

Sources of Funding: This work was supported by a National Institutes of Health T32 Training Grant 5T32AR007176 (RH; PI Steven B. Abramson, MD), a Fellowship Award in Osteoarthritis from the Arthritis Foundation New York Chapter (RH) and Pilot Award from the Clinical and Translational Science Institute of NYU School of Medicine (RH). MHP is supported in part by CTSA grant UL1TR000038 from the National Center for the Advancement of Translational Science, National Institutes of Health.

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KEY POINTS

1. In this study, older men with gout had a significantly increased prevalence of knee osteoarthritis.
2. Older men with asymptomatic hyperuricemia may also have an increased prevalence of knee osteoarthritis.
3. The association between gout, hyperuricemia and osteoarthritis, including the direction of effect of any possible relationship, deserves further study.

Figure 1. Patient Recruitment/Enrollment Flow Diagram

Figure 2. Prevalence of knee OA, and impact of BMI on knee OA among control, AH and gout groups

A, Presence of gout predicts increased prevalence of knee OA. Control, AH and gout subjects were assessed for presence of knee OA using ACR Clinical/Radiographic or Clinical OA criteria, as indicated (* $P < 0.05$ vs. control group). *B, Presence of gout predicts increased prevalence of knee OA among non-obese patients.* Control, AH and gout subjects were stratified into non-obese (BMI < 30) and obese (BMI ≥ 30) subgroups, and the prevalence of knee OA (ACR Clinical/Radiographic criteria) was determined for each subgroup (* $P < 0.05$ vs. corresponding control group).

Figure 3. Impact of cartilage crystal deposition and acute gout attacks on presence of knee OA

A, Presence of MSU crystal deposition in MTP but not knee joints correlates with prevalence of knee OA. Knees and 1st MTP joints were examined for crystal deposition by MSKUS. White columns indicate patients with no overt crystal deposition at the examined sites; black columns indicate the presence of crystal deposition. B, Presence of knee OA correlates with presence of macroscopic MSU crystal deposition identified by MSK-US, but not with presence of crystals in OA-affected knee joints. Black columns indicate the presence of crystals in any joint examined (all knees and 1st MTPs); white bars indicate the presence of crystals in OA-affected knee joints only. C, Prior gout attacks in affected knees do not correlate with presence of knee OA. Gout patients with self-report of 1 gouty attacks in the knees (n=16), vs. a history of gouty attacks only in locations other than the knees (n=9) were assessed for the presence of knee

Table 1

Patient Characteristics

Characteristics	Control (n=25)	AH (n=25)	Gout (n=25)	Overall P Value
Age in years, mean (SD)	68.5 (7.4)	67.4 (8.8)	72.0 (8.9)	0.146
Race/Ethnicity, number (%)				
African-American	8 (32.0)	9 (36.0)	14 (56.0)	0.360*
Caucasian	9 (36.0)	10 (40.0)	8 (32.0)	
Hispanic	8 (32.0)	5 (20.0)	3 (12.0)	
Years of education, mean (SD)	14.5 (2.5)	13.8 (3.4)	12.6 (3.5)	0.048
BMI, mean (SD)	27.1 (3.7)	31.2 (7.1)	31.5 (4.1)	0.005
eGFR in mL/min, mean (SD)	81.1 (20.5)	75.4 (15.6)	62.2 (18.0)	0.002
CV disease, number (%)	5 (20.0)	8 (32.0)	11 (44.0)	0.191*
Hypertension, number (%)	15 (60.0)	21 (84.0)	21 (84.0)	0.072*
Diabetes mellitus, number (%)	12 (48.0)	13 (52.0)	11 (44.0)	0.852*
Smoker, number (%)				
Current	7 (28.0)	3 (12.0)	1 (4.0)	0.067 [†]
Past (last 10 years)	7 (28.0)	5 (20.0)	2 (8.0)	0.189
Alcoholic drinks/week, mean (SD)				
Beer	1.5 (4.8)	1.4 (3.1)	1.4 (4.9)	0.641
Liquor	1.1 (4.2)	1.4 (3.3)	3.1 (14.0)	0.457
Wine	0.4 (1.3)	1.8 (4.2)	0.9 (3.1)	0.543
Knee Activity [0–6], mean (SD)	4.0 (2.0)	3.0 (2.1)	3.9 (1.9)	0.141
Serum UA in mg/dL, mean (SD)	5.5 (0.8)	8.1 (1.0)	7.3 (2.4)	<0.001
Diuretic use, number (%)	6 (24.0)	13 (52.0)	11 (44.0)	0.115
Colchicine use, number (%)	0 (0)	0 (0)	7 (28.0)	0.001[†]
ULT use, number (%)	0 (0)	0 (0)	11 (44.0)	<0.001[†]
Clinic usage-number of ambulatory care visits annually, mean (SD)	12 (11.8)	16.6 (11.4)	13.5 (9.4)	0.158

* Chi-Square test reported.

[†] Fisher's Exact test reported. Otherwise, Kruskal-Wallis reported.

Table 2

Odds Ratios of Knee OA Diagnosis by Group Comparisons with and without Adjustment for BMI

	Unadjusted Odds Ratio (95% CI)	P Value	BMI-Adjusted Odds Ratio (95% CI)	P Value
Knee OA (ACR Clinical/Radiographic Criteria)				
Gout – Control *	5.46 (1.63, 18.36)	0.006	3.80 (1.06, 13.57)	0.040
Gout - AH	1.96 (0.62, 6.19)	0.251	1.92 (0.59, 6.29)	0.281
AH - Control	2.79 (0.86, 9.01)	0.087	1.98 (0.57, 6.88)	0.284
Knee OA (ACR Clinical Criteria)				
Gout - Control	5.09 (1.45, 17.92)	0.011	3.31 (0.88, 12.46)	0.076
Gout - AH	3.69 (1.05, 12.96)	0.041	3.69 (1.00, 13.57)	0.050
AH - Control	1.38 (0.45, 4.20)	0.572	0.90 (0.27, 3.03)	0.863
Bilateral knee OA (Clinical / Radiographic Criteria)				
Gout - Control	6.61 (1.92, 22.73)	0.003	4.41 (1.21, 16.11)	0.025
Gout - AH	5.46 (1.63, 18.36)	0.006	6.03 (1.68, 21.62)	0.006
AH - Control	1.21 (0.36, 4.07)	0.758	0.73 (0.19, 2.85)	0.652
Bilateral knee OA (Clinical Criteria)				
Gout - Control	8.14 (2.29, 28.90)	0.001	5.22 (1.38, 19.71)	0.015
Gout - AH	5.46 (1.63, 18.36)	0.006	6.22 (1.70, 22.76)	0.006
AH - Control	1.49 (0.43, 5.17)	0.530	0.84 (0.21, 3.43)	0.807

* Pre-specified primary outcome

Table 3

Knee OA Severity (by group)

Outcome	Control	AH	Gout	<i>P</i> Value ¹
Kellgren-Lawrence grade				
Clinical-radiographic OA *				
All knees, mean (SD)	2.38 (0.91)	2.93 (1.01)	3.50 (0.72)	0.001
Right knees only, mean (SD)	2.00 (0.82)	3.00 (1.15)	3.58 (0.67)	0.0007
Left knees only, mean (SD)	2.75 (0.96)	2.86 (1.07)	3.42 (0.79)	0.09
Clinical OA				
All knees	1.14 (0.25)	1.96 (0.26) ²	2.32 (0.27)	0.005
Right knees only	1.00 (0.30)	2.08 (0.37)	2.42 (0.38)	0.02
Left knees only	1.27 (0.41)	1.86 (0.36)	2.1 (0.39)	0.18
Bilateral knee OA				
Clinical/Radiographic, number (%)	7 (28.0)	8 (32.0)	18 (72.0)	0.002
Clinical, number (%)	6 (24.0)	8 (32.0)	18 (72.0)	0.001
WOMAC				
All categories, mean (SD) ³	72.8 (65.7)	67.0 (74.4)	101.3 (81.2)	0.214
Pain, mean (SD) ⁴	22.0 (20.1)	18.8 (25.1)	32.2 (27.4)	0.141
Stiffness, mean (SD) ⁴	26.1 (29.3)	25.4 (28.1)	34.0 (33.4)	0.647
Function, mean (SD) ⁴	24.7 (24.9)	22.8 (25.5)	35.2 (26.3)	0.188
Maximum reported score/group ³	174	240	263	–
RAPID3, mean (SD)⁵	7.3 (6.6)	6.5 (6.9)	9.9 (5.6)	0.081

¹ Gout vs. Control;² P=0.03, control vs AH.³ Range 0–300⁴ Range 0–100⁵ Range 0–30

* Pre-specified primary outcome