Are joints affected by gout also affected by osteoarthritis?

Edward Roddy, Weiya Zhang, Michael Doherty

Objectives: To determine whether joints affected by gout are also affected by osteoarthritis (OA).

Methods: A postal questionnaire was sent to all adults aged over 30 years registered with two general practices. The questionnaire assessed a history of gout (doctor diagnosed, or episodes suggestive of acute crystal synovitis) and medication use. Patients who possibly had gout attended for clinical assessment to verify the diagnosis on clinical grounds and assess the distribution of joints affected by acute attacks of gout and OA. Adjusted odds ratios (aOR) and 95% confidence intervals (CI) were calculated between the history of an acute attack of gout and the presence of OA at an individual joint adjusted for age, gender, body mass index and prior diuretic use in a binary logistic regression model.

Results: A total of 4249 completed questionnaires were returned (32%). From 359 attendees, 164 cases of gout were clinically confirmed. A highly significant association existed between the site of acute attacks of gout and the presence of OA (aOR 7.94; 95% CI 6.27, 10.05). Analysis at individual joint sites revealed a significant association at the first metatarsophalangeal joint (aOR 2.06; 95% CI 1.28, 3.30), mid-foot (aOR 2.85; 95% CI 1.34, 6.03), knee (aOR 3.07; 95% CI 1.05, 8.96) and distal interphalangeal joints (aOR 12.67; 95% CI 1.46, 109.91).

Conclusion: Acute attacks of gout at individual joint sites are associated with the presence of clinically assessed OA at that joint suggesting that OA may predispose to the localised deposition of monosodium urate crystals.

Gout is one of the most common inflammatory arthritides with a community prevalence of 1–2%. It displays a characteristic pattern of joint involvement, in particular, a striking tendency to affect the first metatarsophalangeal (1st MTP) joint. It tends to affect also distal peripheral joints such as the mid-tarsal joints, ankles, knees, interphalangeal (IP) finger joints, wrists and elbows, with axial joints such as the hips, shoulders and spine only very rarely affected. The reason for this characteristic distribution of affected joints is not understood. However, case reports and small hospital-based case series report the occurrence of gout at joint sites affected by osteoarthritis (OA) especially the 1st MTP joint and distal IP finger joints. This suggests that changes in the osteoarthritic joint may predispose to monosodium urate (MSU) crystal formation. Furthermore, a Polish hospital-based study of 262 subjects with gout found an association between gout and radiographic evidence of OA at the 1st MTP joints, tarsal joints and knees. This study did not, however, consider upper limb joints and also runs the risk of inherent bias as a hospital-based population, whereas OA is managed largely in primary care.

We undertook this community-based study in order to determine whether joints affected by gout are also affected by OA, both overall and at individual joint sites.

METHODS

The study was undertaken in two general practices in Nottingham, nested within a case–control study. It consisted of two phases: (1) a postal questionnaire survey, and (2) a face-to-face clinical assessment. The study was approved by the Nottingham Local Research Ethics Committee 2 and written consent to participate was obtained from participants who attended for clinical assessment.

Postal questionnaire

Each practice drew up a list of all registered adults over the age of 30 years, excluding those with a history of major psychiatric disease, dementia or recently diagnosed malignancy. A questionnaire was then mailed to all listed individuals with a pre-paid envelope included for their reply. Possible cases of gout were identified by two questions:

- Have you ever been diagnosed with or suffered from gout?
- Have you ever suffered from an acute attack of arthritis that was severely painful, was associated with a red and swollen joint, came on suddenly reaching its peak severity within 24 h and then went away completely within 3 weeks? (ie, a typical attack of crystal synovitis?)

Age of onset of gout, current use of allopurinol and diuretic use prior to the onset of gout were requested in addition to recording standard demographic information, weight and height.

Following the first round of mailing, in order to enhance a poor response rate, an abbreviated questionnaire was mailed out to non-respondents in one practice.

Clinical assessment

All subjects that indicated a previous diagnosis of gout or a history of acute self-limiting attacks of painful, red, swollen joints in their questionnaire (ie, potential cases) were invited to attend a clinical assessment. At this visit, the subject’s joint problems were reviewed by a physician with special training in gout (ER) and the most likely diagnosis was made on clinical grounds. The diagnosis of gout was further assessed according to American Rheumatism Association preliminary criteria for the acute arthritis of primary gout. Each subject was asked where (ie, individual joint sites) they had ever experienced acute attacks of gout, for example, 1st MTP joint, mid-foot, ankle, knee, hip, finger and thumb IP joints, thumb-base (ie, first carpo-metacarpal joint), wrist, elbow or shoulder (36 joints were assessed OA at that joint suggesting that OA may predispose to the localised deposition of monosodium urate crystals.

Abbreviations: aOR, adjusted odd ratio; BMI, body mass index; CI, confidence interval; DIP, distal interphalangeal; IP, interphalangeal; MSU, monosodium urate; MTP, metatarsophalangeal; OA, osteoarthritis, OR, odds ratio; PIP, proximal interphalangeal
in total for each subject). Subjects were also asked to specify whether attacks had affected the left or right side at each individual joint site.

Subjects were systematically examined for the presence of OA at all joint sites. OA of the hip was considered to be present if the subject had had a hip replacement or there was restriction of passive internal rotation of the hip with the hip flexed at 90°. The knee joint was examined for five features: joint replacement, restricted passive flexion and extension, crepitus, joint line tenderness and effusion. OA of the knee was defined according to two criteria: (1) the subject had had a knee replacement, or (2) there was restricted passive flexion/extension with either crepitus or joint line tenderness. At other joint sites, OA was defined as the presence of restricted passive movement or bony swelling or crepitus.

Participants were also examined for the presence of tophi. These were classified as definite (asymmetric white/yellow swellings on pulling the overlying skin taut) or possible (asymmetric nodular swellings without white/yellow discoloration). Blood was taken for measurement of serum urate and creatinine.

**Statistical analysis**

The unit of analysis was considered to be the joint rather than the subject. Two analyses were undertaken.

First, the crude odds ratio (OR) and 95% confidence interval (CI) between the presence of OA at an individual joint and a history of an acute attack of gout at that joint were calculated for all joint sites combined. This analysis included 5904 individual joints (ie, all 36 joints examined in 164 individuals). Whether a joint had been affected by an acute attack of gout was then entered as the dependent variable into a forward stepwise logistic regression model with age (decades), gender, body mass index (BMI; >30 kg/m²), previous diuretic use and presence of OA at that joint as independent variables and an adjusted OR (aOR) and 95% CI were calculated. In order to investigate the influence of disease duration on the relationship between the site of acute attacks of gout and the presence of OA, subjects were grouped according to tertiles of disease duration and the crude and adjusted ORs calculated for each tertile.

Secondly, crude and adjusted ORs were then calculated at each individual joint site (left and right sides combined). As acute attacks of gout in the finger IP joints were an uncommon occurrence, analyses were performed for three anatomical units: distal IP (DIP) joint row, proximal IP (PIP) joint row and the whole hand (ie, acute attacks of gout and OA occurring anywhere within that unit).

**RESULTS**

Questionnaires were mailed to a total of 13 684 individuals, and 4249 completed responses were returned; 294 were notified as being sent to the wrong address. The adjusted response rate was, therefore, 32% (fig 1).

A total of 488 respondents reported acute attacks of self-limiting synovitis and/or a diagnosis of gout: 264 had been given a diagnosis of gout. Three hundred and fifty-nine attended the clinical assessment (75%). Of these, 175 reported being diagnosed with gout by a doctor. This was thought to be the correct diagnosis in 145 (83%). A further 19 subjects were thought to have gout but had never consulted a doctor. Therefore, 164 subjects were identified as having gout. Characteristics of the 164 subjects with gout are shown in table 1.

The most common site of acute attacks of gout was the 1st MTP joint followed by the mid-foot, ankle and knee (table 2). Upper limb involvement was uncommon. Involvement of left and right sides was similar at all joint sites.

Analysis of all 5904 individual joint sites combined found a highly significant association between the site of acute attacks of gout and the presence of OA after adjustment for confounding factors (aOR 7.94; 95% CI 6.27, 10.05) (table 3).

On indirect comparison of the three tertiles of disease duration, the strength of association between sites of acute attacks of gout and the presence of OA appeared similar (table 4). ORs were numerically smaller with increasing disease duration, although there was considerable overlap of 95% CI.

Analysis at individual joint sites revealed a significant association between acute attacks of gout and the presence of OA at the 1st MTP joint (aOR 2.06; 95% CI 1.28, 3.30), mid-foot (aOR 2.85; 95% CI 1.34, 6.03), knee (aOR 3.07; 95% CI 1.05, 8.96) and DIP joints (aOR 12.67; 95% CI 1.46, 109.91) after adjustment for confounding variables (table 5).

**DISCUSSION**

A strong association was seen between joint sites affected by acute attacks of gout and the presence of clinically assessed OA. When this relationship was assessed at individual joint sites, significant associations were seen at the 1st MTP, mid-foot, knee and finger DIP joints after adjustment for confounding variables. These data support the hypothesis that the presence of OA at an individual joint site predisposes to the formation of urate crystals at that site as suggested by a number of case reports and small case series and one Polish hospital-based study. This latter study found a significant correlation between gout and radiographic presence of OA at the 1st MTP joint, mid-foot and knee in 262 subjects with gout. The current study is the first to evaluate this question in a community-based sample and to consider the upper limb joints.

A number of mechanisms have been suggested to explain an association between the sites of acute attacks of gout and OA, including: mechanical shock; changes in cartilage and synovial proteoglycans; epitaxial MSU crystal formation on cartilage fragments; and transient increases in the urate concentration of resolving synovial effusions owing to the differential permeability of synovium to urate and water, which might encourage nucleation and precipitation of MSU crystals. An association between OA and calcium crystal deposition is well recognised. Community studies have confirmed a positive association between knee OA and chondrocalcinosis. There is an increased incidence of calcium pyrophosphate dihydrate and basic calcium phosphate crystals in synovial fluid and cartilage from OA joints, and also local mechanical factors (including joint hypermobility and instability, joint motion, ligamentous laxity and joint damage from surgery and trauma) are known to predispose to localised secondary deposition of calcium pyrophosphate dihydrate crystals in the context of joint damage. It is possible that OA results in changes in tissue factors, either an increase in promoters or a reduction in inhibitors of crystal nucleation and growth, which might predispose not just to calcium crystal but also to MSU crystal deposition. It has also been suggested that the predilection of gouty arthritis and tophi for cooler extremities such as the hallux, fingers and ears and the rarity of gout at axial joints such as the hip and shoulder could be explained by the reduction seen in the solubility of urate with decreasing temperature. However, this does not explain why gout should preferentially affect the MTP joint of the great toe rather than the lesser toes or the great toe IP joint.

The major limitation to our study is the low overall response rate to the postal questionnaire. In addition to 164 gout cases identified, there were a further 89 subjects who reported suffering from gout in the questionnaire but did not consent to
clinical assessment. Another possible limitation is the use of a clinical case definition for gout. The recent EULAR (the European League Against Rheumatism) recommendations for the diagnosis of gout found that the rapid development of severe pain, swelling, tenderness and erythema is highly suggestive of crystal inflammation, although not specific for gout; however, 1st MTP joint involvement markedly increases the specificity of this clinical composite. Although it is possible that some of the acute attacks that were presumed to be due to gout were, in fact, due to other crystals, most commonly calcium pyrophosphate; this is unlikely to have accounted for much misclassification given the sites of involvement observed. Without doubt, the gold standard for the diagnosis of gout is the identification of crystals on aspirates from synovial fluid or tophus. However, while intercritical joint aspiration is a useful diagnostic technique, the requirement to undergo aspiration may have reduced further the number of individuals.

**Table 2** frequency of acute attacks of gout at each joint site

<table>
<thead>
<tr>
<th>Joint</th>
<th>Left (% of subjects)</th>
<th>Right (% of subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st MTP joint</td>
<td>61</td>
<td>66</td>
</tr>
<tr>
<td>Mid-foot</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>Ankle</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Knee</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Hip</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DIP joints</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>PIP joints</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Thumb-base</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hand</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Wrist</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Elbow</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Shoulder</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

MTP, metatarsophalangeal; DIP, distal interphalangeal; PIP, proximal interphalangeal.

**Table 3** Odds ratio (OR) and 95% confidence interval (CI) between the site of acute attacks of gout and presence of OA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of OA in the index joint</td>
<td>6.76 (5.39, 8.46)</td>
<td>7.94 (6.27, 10.05) *&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusted for age (decades), gender, BMI (≥ 30 kg/m²) and prior diuretics use using a forward step-wise binary logistic regression model with gout in the index joint as the dependent variable.

**Table 4** Odds ratios (OR) and 95% confidence interval (CI) between attacks of gout and presence of OA stratified by disease duration (tertiles)

<table>
<thead>
<tr>
<th>Disease duration (years), mean (SD)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tertile 1 (2.9 (2.2)</td>
<td>7.39 (4.80, 11.37)</td>
<td>10.12 (6.29, 16.29)</td>
</tr>
<tr>
<td>Tertile 2 (10.2 (2.1)</td>
<td>7.19 (4.97, 10.41)</td>
<td>8.22 (5.61, 12.06)</td>
</tr>
<tr>
<td>Tertile 3 (25.9 (8.4)</td>
<td>6.02 (4.11, 8.80)</td>
<td>6.45 (4.38, 9.48)</td>
</tr>
</tbody>
</table>

*Adjusted for age (decades), gender, BMI (≥ 30 kg/m²) and prior diuretics use using a forward step-wise binary logistic regression model with gout in the index joint as the dependent variable.

**Table 5** Odds ratio (OR) and 95% confidence interval (CI) between acute attacks of gout and presence of OA for each joint site (left and right combined)

<table>
<thead>
<tr>
<th>Joint</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st MTP joint</td>
<td>1.73 (1.10, 2.73)</td>
<td>2.06 (1.28, 3.30) 0.003</td>
</tr>
<tr>
<td>Mid-foot</td>
<td>2.58 (1.24, 5.35)</td>
<td>2.85 (1.34, 6.03) 0.006</td>
</tr>
<tr>
<td>Ankle</td>
<td>4.08 (0.94, 17.73) NS</td>
<td></td>
</tr>
<tr>
<td>Knee</td>
<td>2.98 (1.02, 8.68)</td>
<td>3.07 (1.05, 8.96) 0.040</td>
</tr>
<tr>
<td>Hip</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>DIP joints</td>
<td>12.50 (1.44, 108.46) 12.67 (1.46, 109.91) 0.021</td>
<td></td>
</tr>
<tr>
<td>PIP joints</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Thumb-base</td>
<td>2.90 (0.86, 9.83)</td>
<td>NS</td>
</tr>
<tr>
<td>Hand</td>
<td>3.04 (0.24, 9.37)</td>
<td>NS</td>
</tr>
<tr>
<td>Elbow</td>
<td>1.16 (0.14, 9.37)</td>
<td>NS</td>
</tr>
<tr>
<td>Shoulder</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Adjusted for age (decades), gender, BMI (≥ 30 kg/m²) and prior diuretics using a forward step-wise binary logistic regression model with gout in the index joint as the dependent variable.

NS, not significant; MTP, metatarsophalangeal; DIP, distal interphalangeal; PIP, proximal interphalangeal.
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