Level of Agreement with the Microscopic Analysis of Joint Aspirate for the Diagnosis of Gout in the Lower Extremity

Alexis Zavisanos, MD*
Todd Hasenstein, DPM†
Andrew J. Meyr, DPM‡

Background: Although clinical findings, laboratory serum markers, and radiographic images are also used, the purported gold standard or standard reference test for the diagnosis of gout is microscopic analysis of aspirated joint fluid. This observational investigation sought to identify the level of agreement with the microscopic analysis of joint fluid aspirate for the diagnosis of gout in the lower extremity between two departments in a single health-care center.

Methods: A retrospective medical record review identified consecutive patients seen for suspected gout who underwent diagnostic joint aspiration. Patients were included if a lower-extremity joint synovial fluid sample was obtained and were excluded if they were not independently evaluated by both the departments of rheumatology and pathology. We categorized the documented joint fluid findings into four groups: no crystals, sodium urate crystals, calcium pyrophosphate dihydrate crystals, or both sodium urate and calcium pyrophosphate dihydrate crystals. We defined a ''clinically significant disagreement'' as one department observing any type of crystals and the other department observing no crystals.

Results: We observed a clinically significant disagreement rate of 23.26% (intraclass correlation coefficient = 0.496). The department of rheumatology was more likely to observe the presence of crystals in a sample compared with the department of pathology (88.37% versus 65.12%; $P = .02$).

Conclusions: These results provide evidence that microscopic analysis of joint fluid aspirate might lack the accuracy and reliability needed to be considered a gold standard diagnostic test for gout in the lower extremity. (J Am Podiatr Med Assoc 110(4): 1-4, 2020)

Although clinical findings, laboratory serum markers, and radiographic images are also used, the purported gold standard or standard reference test for the diagnosis of gout is microscopic analysis of aspirated joint fluid.[1-9] Gout has historically been defined by the presence of needle-shaped monosodium urate crystals, which are negatively birefringent when viewed under polarizing light parallel to the axis of the microscope lens. There is the potential for subjectivity within this definition, however, considering that it is typically made by one physician looking at one sample underneath a microscope.[10-13] In fact, our group has previously shown relative subjectivity with a different gold standard diagnostic test relying on similar microscopic analysis.[14]

The objective of this retrospective, observational investigation was to identify the level of agreement with the microscopic analysis of joint fluid aspirate for the diagnosis of gout in the lower extremity between two departments in a single health-care center.

Materials and Methods

After receiving approval from the Temple University Hospital institutional review board, a retrospective medical record review was performed to identify consecutive patients seen in consultation by our

*Department of Rheumatology, Coordinated Health, Allentown, PA.

†Temple University Hospital Podiatric Surgical Residency Program, Philadelphia, PA.

‡Department of Podiatric Surgery, Temple University School of Podiatric Medicine, Philadelphia, PA.

Corresponding author: Andrew J. Meyr, DPM, Department of Podiatric Surgery, Temple University School of Podiatric Medicine, 8th at Race St, Philadelphia, PA 19107. (E-mail: ajmeyr@gmail.com)

institution's department of rheumatology for suspected gout with performance of a diagnostic joint aspiration. Patients were included if a synovial fluid sample was obtained from the lower-extremity joint and were excluded if they were not independently evaluated by both the departments of rheumatology and pathology. At our institution it is common clinical practice for all synovial fluid samples to be sent to and analyzed by the department of pathology. However, if performing the aspiration as part of their consultation, rheumatologists will routinely perform their own microscopic joint fluid analysis and reach their own diagnosis before and independent of the official report of the pathologist.

As a primary outcome measure, the initial department of rheumatology documentation of the joint fluid findings were compared with the official department of pathology documentation for the sample. We categorized the documented joint fluid findings into four groups: no crystals, sodium urate crystals, calcium pyrophosphate dihydrate crystals, or both sodium urate crystals and calcium pyrophosphate dihydrate crystals. We defined "any disagreement" as findings between the two departments not in the same category, and we defined "clinically significant disagreement" as one department observing any type of crystals and the other department observing no crystals.

Basic descriptive statistics of percentage agreement and disagreement were performed, in addition to an intraclass correlation coefficient (ICC). A two-tailed Fisher exact test was also performed for analysis of the clinically significant disagreement data. The level of statistical significant was set at $P = .05$.

Results

We identified 43 joint fluid samples from 35 patients who met the study inclusion and exclusion criteria. Twenty-seven samples (62.79%) were from men (mean ± SD age, 64.05 ± 11.27 years; age range, 35–94 years). In terms of race, 33 samples (76.74%) were from black/African American patients, five (11.63%) were from white patients, and five (11.63%) were from patients of other races. In terms of ethnicity, seven samples (16.28%) were from Hispanic/Latino patients. All of the 43 joint fluid samples came from the knee joint.

The department of pathology observed no crystals in 15 samples (34.88%), sodium urate crystals in 23 (53.49%), calcium pyrophosphate dehydrate crystals in three (6.98%), and both sodium urate and calcium pyrophosphate dehydrate crystals in two (4.65%). The department of rheumatology observed no crystals in five samples (11.63%), sodium urate crystals in 28 (65.12%), calcium pyrophosphate dehydrate crystals in two (4.65%), and both sodium urate and calcium pyrophosphate dehydrate crystals in eight (18.60%).

There was absolute agreement between the two departments in 26 samples (60.47%), so an any disagreement rate of 39.53%. This had a corresponding ICC of 0.670. There was clinically significant agreement between the two departments in 33 samples (76.74%), so a clinically significant disagreement rate of 23.26%. This had a corresponding ICC of 0.496.

The department of rheumatology was more likely to observe the presence of crystals in a sample compared with the department of pathology (88.37% versus 65.12%; $P = .02$).

Discussion

As with any scientific investigation, critical readers are encouraged to review the study design and results and reach their own conclusions; the following represents our conclusions based on the preceding results. As scientists we also never consider data to be definitive, but we do think that these results are worthy of attention and future investigation.

First, we observed a higher-than-hypothesized rate of disagreement between the rheumatology and pathology departments when analyzing joint fluid aspirate for the presence of gout in the lower extremity. The rate of any disagreement with respect to the sample was close to 40%, and in approximately 20% of cases there was a clinically significant disagreement that would have the potential to affect subsequent patient treatment interventions. The ICC of 0.496 with respect to agreement on the presence of crystals indicates a "good" level of reliability for this diagnostic test, but perhaps below the standard typically used for a gold standard diagnostic test.[15] This finding may provide evidence for the personal evaluation of synovial samples when a joint aspiration is performed, and the need for the development of comprehensive criteria on which to base a reliable diagnostic protocol.

As reported by Gordon et al,[16] there is low sensitivity and reliability for detection of either sodium urate or pyrophosphate dehydrate crystals by light microscope because the crystals are either too small or in too low concentration (diluted) to be identified,[16-18] leading to a false-negative result. On the other hand, the low specificity is likely

attributed to the lack of experience of the person performing the microscopic analysis.[19] Dieppe and Swan[10] mentioned that specificity has reasonable solutions via experience, technique, and technology advance; however, sensitivity is not an on-off phenomenon with the presence of crystals but will always have to reach a detection threshold.

We also noted that the department of rheumatology was more likely to observe the presence of crystals in a joint fluid sample compared with the department of pathology (88.37% versus 65.12%; $P = .02$). This potentially means that pathologists are underdiagnosing gout, rheumatologists are overdiagnosing it, or some combination of the two. It is interesting to consider that pathologists are performing the analysis with little adjuvant clinical information, whereas rheumatologists are examining the patient and performing the aspiration. One might hypothesize that this clinical information could influence the pretest probability and interpretation of the test, although that was not specifically studied with this design. We believe that this could represent an interesting avenue for future investigations.

All scientific investigations have limitations, and this one had several important ones to consider. First, data were collected from a limited number of patients and from a single health-care center, so the results might not be representative of a broader population sampling. Second, all retrospective studies have inherent limitations. We were dependent on physician documentation during data collection, and any inaccuracies in this would result in inaccuracy of our data analysis and interpretation. Third, the four categories that we derived for potential findings of joint fluid aspirate may not be universally compatible with contemporary clinical practice. Fourth, all joint aspiration samples obtained were from the knee. Although we attempted to collect data from the entire lower extremity, no sample that met both the inclusion and exclusion criteria produced samples other than the knee. This is likely due to the fact in our hospital, podiatric medicine is called for any pathology involving the joints of the foot or ankle and the podiatric surgical department does not routinely perform their own microscopic joint fluid analysis. As mentioned previously herein, the sensitives of crystal detention can be affected by the size and concentration of the crystals, which could result in a different conclusion when examining the first metatarsophalangeal and ankle joints separately, given that these joints are smaller, which allows the concentration to accumulate faster than in the knee. And fifth, this was not a study of clinical outcomes. We cannot say how any of the potential disagreements that we observed actually affected the diagnosis and treatment of patients.

In conclusion, the results of this investigation provide evidence that microscopic analysis of joint fluid aspirate might lack the accuracy and reliability needed to be considered a gold standard diagnostic test for gouty arthritis. We hope that these results lead to future investigations into the diagnosis and treatment of gout.

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References

1. Neogi T, Jansen TL, Dalbeth N, et al: 2015 Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis **74:** 1789, 2015.
2. Sivera F, Andres M, Falzon L, et al: Diagnostic value of clinical, laboratory, and imaging findings in patients with clinical suspicion of gout: a systematic literature review. J Rheumatol Suppl **92:** 3, 2014.
3. Schlesinger N: Diagnosis of gout: clinical, laboratory, and radiographic findings. Am J Manag Care **11:** S443, 2005.
4. Graf SW, Buchbinder, Zochling J, et al: The accuracy of methods for urate crystal detection in synovial fluid and the effect of sample handling: a systematic review. Clin Rheumatol **32:** 225, 2013.
5. Lumbreras B, Pascual E, Frasquet J, et al: Analysis for crystals in synovial fluid: training of the analysts results in high consistency. Ann Rheum Dis **64:** 612, 2015.
6. Pascual E, Batlle-Gualda E, Martinez A, et al: Synovial fluid analysis for diagnosis of intercritical gout. Ann Intern Med **131:** 756, 1999.
7. Wijnands JM, Boonen A, Arts IC, et al: Large epidemiologic studies of gout: challenges in diagnosis and diagnostic criteria. Curr Rheumatol Rep **13:** 167, 2011.
8. Dalberth N, Schumacher HR, Fransen J, et al: Survey definitions of gout for epidemiological studies: comparison with crystal identification as the gold standard. Arthritis Care Res (Hoboken) **68:** 1894, 2016.
9. Houk JL: "Joint Fluid," in *Oxford Textbook of Rheumatology*, 3rd Ed, ed by DA Isenberg, PJ Maddison, P Woo, et al, p 499, Oxford University Press, New York, 2004.
10. Dieppe P, Swan A: Identification of crystals in synovial fluid. Ann Rheum Dis **58:** 261, 1999.
11. von Essen R, Holtta AM, Pikkarainen R. Quality control of synovial fluid crystal identification. Ann Rheum Dis **57:** 107, 1998.
12. Schumacher HR, Sieck MS, Rothfuss S, et al: Reproducibility of synovial fluid analysis: a study among four laboratories. Arthritis Rheum **29:** 770, 1986.
13. Lumbreras B, Pascual E, Frasquet J, et al: Analysis for

crystals in synovial fluid: training of the analysts results in high consistency. Ann Rheum Dis **64:** 612, 2005.

14. Meyr AJ, Singh S, Zhang X, et al: Statistical reliability of bone biopsy for the diagnosis of diabetic foot osteomyelitis. J Foot Ankle Surg **50:** 663, 2011.
15. Guyatt G, Rennie D, Meade MO, et al: *Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice*, 2nd Ed, McGraw-Hill, New York, 2008.
16. Gordon C, Swan A, Dieppe PA: Detection of crystals in synovial fluids by light microscopy: sensitivity and reliability. Ann Rheum Dis **48:** 737, 1989.
17. Swan AJ, Chapman B, Heap P, et al: Submicroscopic crystals in osteoarthritic synovial fluids. Ann Rheum Dis **53:** 467, 1994.
18. Bjelle A, Crocker P, Willoughby D: Ultramicrocrystals in pyrophosphate arthropathy: crystal identification and case report. Acta Med Scand **207:** 89, 1980.
19. Dieppe P, Swan A: *The Identification of Crystals in Synovial Fluid*, University of Bristol, Bristol, England, 1998.