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Original article

Test characteristics of Raman spectroscopy integrated with polarized light microscopy for the diagnosis of acute gouty arthritis

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ABSTRACT

Objectives. – We studied the performance of Raman spectroscopy integrated with polarized light microscopy (iRPolM) as a next-generation technique for synovial fluid analysis in gout.
Methods. – This is a prospective study, including consecutive synovial fluid samples drawn from any peripheral swollen joint. Diagnostic accuracy was compared to the 2015 ACR/EULAR Gout classification criteria as a reference test and to polarized light microscopy (PLM) analysis by a rheumatologist. Synovial fluid was analysed with iRPolM after unblinding the PLM results.
Results. – Two hundred unselected consecutive patient samples were included in this study. Validation against clinical criteria: 67 patients were classified as gout according to 2015 ACR/EULAR classification criteria. Compared to the 2015 ACR/EULAR gout classification criteria, iRPolM had a sensitivity of 77.6% (95% CI: 65.8–86.9), specificity of 97.7% (95% CI: 93.5–99.5), positive predictive value (PPV) of 94.5% (95% CI: 84.9–98.2), negative predictive value (NPV) of 89.7% (95% CI: 84.7–93.1), an accuracy of 91.0% (95% CI: 86.2–94.6), a positive likelihood ratio of 34.4 (95% CI: 11.16–106.10) and a negative likelihood ratio of 0.23 (95% CI: 0.15–0.36). Validation against PLM: 55 samples were positive for MSU according to PLM. The interrater agreement between PLM and iRPolM was near perfect ($\kappa = 0.90$). The sensitivity of iRPolM to identify MSU in PLM-positive samples was 91.2% (95% CI: 80.7–97.1), the specificity was 97.6% (95% CI: 93.0–99.5), the PPV was 94.6% (95% CI: 85.0–98.2), NPV was 96.0% (95% CI: 91.2–98.2) and the accuracy was 95.6% (95% CI: 91.4–98.2). The positive likelihood ratio was 37.4 (95% CI: 12.20–114.71), and the negative likelihood ratio was 0.09 (95% CI: 0.04–0.21).
Conclusion. – iRPolM is a promising next-generation diagnostic tool for rheumatology by diagnosing gout with high specificity, increased objectivity, and a sensitivity comparable to PLM.

1. Introduction

Analysis of synovial fluid with polarized light microscopy (PLM) for the presence of monosodium urate (MSU) needles is internationally recognized as a definitive proof in the diagnosis of gout [1]. PLM identification of crystals in general is challenging, as shown by poor interrater reliability, lack of proper equipment or training, and poor reproducibility [2–6]. Size differences, the presence of other crystalline material, artifacts such as glass slivers, and cellular uptake of microcrystals can all pose uncertainties in the clinical analysis of synovial fluids. Furthermore, any technique requiring an expert doing visual analysis via pattern recognition of microscopic images is inherently subjective and can lead to bias [7].

There are multiple methods in development to improve crystal identification in synovial fluid analysis [8,9]. This includes quantitative polarized light microscopy [10], a rapid colorimetric gout detection kit [11], laser desorption/ionization time-of-flight (LDI-ToF) mass spectrometry [12], and multiple applications of Raman spectroscopy [8,13]. These applications of Raman spectroscopy for the diagnosis of gout include a transdermal optical imaging Raman probe [14], a point-of-care Raman spectroscope [15], and stimulated Raman spectroscopy [16]. We previously published a proof-of-principle study in which we demonstrated how hyperspectral Raman imaging could identify not only MSU but also a whole range of novel crystal types in synovial fluid samples [17,18].

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None of all these studies on next-generation synovial fluid analysis were diagnostic accuracy studies, however, and performance measures such as sensitivity, specificity were not reported. With lack of well-tested alternatives, the standard clinical method applied to identify MSU needles has not made any significant advances since the development of PLM analysis for the diagnosis of gouty arthritis in the 1960's.

In this report, we apply an advanced version of our hyperspectral Raman device which is integrated with an ordinary polarized light microscope (iRPolM). This allows for the simultaneous use of both modalities, with localization of crystals using PLM, and chemical identification of the (MSU) crystals with the integrated hyperspectral Raman scanner. The objective of this study was to investigate the performance of iRPolM for the identification of MSU in synovial fluid samples of gout patients. We used the 2015 ACR/EULAR gout classification criteria to classify patients as gout or non-gout and investigated the clinical performance of iRPolM as a diagnostic test in individual patients [19]. Because not every patient with gout is positive for MSU needles, we also investigated the agreement in outcome between PLM and iRPolM in the ability to identify MSU as a technical validation. We expected a high specificity for Raman analysis (> 95%) and a similar performance in terms of sensitivity to PLM.

2. Methods

2.1. Study design and participants

This study was designed as a single-centre, prospective diagnostic accuracy study. Consecutive synovial fluid samples of patients who visited the outpatient clinic of the department of Rheumatology from VieCuri Medical Centre (Venlo, the Netherlands) between April 2022 and December 2022 were included in the study. The clinic is accredited as a gout expertise centre and therefore provides care to a high number of gout patients. Eligible for inclusion were patients above the age of 18 with any swollen peripheral joint who underwent arthrocentesis as part of routine clinical care.

Only clinical waste material was used for this study and no punctures were performed other than those performed for standard diagnostic purposes. Clinical data were retrieved from electronic health records. Patients gave written informed consent to the use of their synovial fluid and clinical data. This study was performed according to good clinical practice guidelines and the Helsinki declaration. Because of the noninvasive nature of this study, the Medical Ethics committee of Maastricht (METC azM/UM) declared that no ethical board examination or registration was required. The hospital board of directors from VieCuri Medical Centre reviewed and approved the study protocol. This study is reported and conducted according to the Standards for Reporting Diagnostic accuracy studies (STARD) guidelines [20].

2.2. Test methods

From each patient sample, a droplet of up to 40 μL of synovial fluid (dependent on joint) was placed on a standard microscope slide (Epredia, Michigan, USA), covered with a coverslip (Menzel-Gläser, Germany), and analysed. A clinical assessor, who was either one of three experienced rheumatologist (TJ, AC, ME) or a supervised physician assistant (TG) analysed each sample for the presence of MSU using a Zeiss Axiolab 5 polarized light microscope (Carl Zeiss AG, Jena, Germany). This is normal clinical practice in our hospital. The test was considered positive for MSU when negative-birefringent needle-shaped crystals were identified in the synovial fluid. For each identification, a score of certainty was given; certainly present, uncertain, or certainly not present. The score of uncertain was given to samples with few, tiny needles which could not be distinguished from possible artifacts.

The samples were then analysed with the Hybriscan iRPoLM (Hybriscan Technologies B.V., Nijkerk, the Netherlands) integrated Raman polarized light microscope. Using this table-top-sized device, birefringent objects were located manually, which were then scanned with the integrated Raman spectroscope. For each object, the Raman spectrum from 0–3600 cm^{-1} was measured for 1 s/pixel with a laser power of approximately 10 mW and a laser with an excitation wavelength of 532 nm. Dependent on crystal size, 60 to 120 pixels were measured, resulting in a total measurement time of 1–2 minutes. The measured spectrum was compared with earlier reported spectra of MSU [15,17]. A patient was considered positive for MSU if at least one crystal with an MSU spectrum could be measured in a sample with iRPolM.

For each patient, the 2015 ACR/EULAR gout classification criteria score was calculated. This score ranges from −6 to 23 points, according to the criteria set, patients are classified as gout if MSU needles are identified in the synovial fluid with PLM or when eight or more points can be awarded. Patients are given points based on clinical presentation, laboratory, and ultrasound imaging. Radiography was not performed in all cases and therefore not used for calculation. Clinical information was available for the rheumatologist or physician assistant (TG/AC/ME/TLJ) when using PLM, as is custom clinical practice. The iRPolM analysis was performed independently from the PLM identification (TN).

We analysed the performance of iRPolM in two scenarios. In the first scenario, diagnostic accuracy of iRPolM was measured against the 2015 ACR/EULAR Gout classification criteria set. These criteria include both PLM and clinical presentation, and in this way, we regard not only gout patients, which are positive for the presence of MSU needles but also the fraction of gout patients without needles in their synovial fluid samples. This method has previously been used in similar studies [21]. We calculated sensitivity, specificity, predictive values, accuracy, and likelihood ratios. In the second scenario, the performance of iRPolM was measured against PLM synovial fluid analysis. We compared how iRPolM scored in samples with or without MSU needles using PLM as a gold standard. This is a measure of analytical performance. We calculated sensitivity, specificity, predictive values, accuracy, likelihood ratios and the interrater reliability between iRPolM and PLM.

2.3. Analysis

The sample size of 200 patients was determined with the sample size estimation for diagnostic test studies [22]. We expected the specificity of MSU identification by Raman spectroscopy to be near 100%, thus the determining factor for sample size is the sensitivity. We estimated the sensitivity of iRPolM for the identification of MSU in gout to be comparable with PLM [2,23]. The prevalence of MSU needles in a similar cohort of patients with swollen joints in a comparable study was 25% [15]. We chose a maximum width of the 95% confidence interval to 10% and the significance level to 0.05.

When the outcome of the PLM analysis was scored as uncertain, microscopy was considered as not performed when calculating the 2015 ACR/EULAR gout classification score, and no points were awarded or subtracted. Missing data were also disregarded in the calculation of the classification score.

All diagnostic accuracy measures, with corresponding 95% confidence intervals, were calculated using 2×2 contingency tables. This was calculated for iRPolM against the 2015 ACR/EULAR gout classification criteria and for iRPolM against MSU identification with PLM. The correspondence between PLM and iRPolM in the identification of MSU was compared with Cohen's Kappa (κ) interrater reliability test. A $\kappa < 0.20$ indicates no agreement, $0.21 < \kappa < 0.39$ indicates a minimal agreement, $0.40 < \kappa < 0.59$

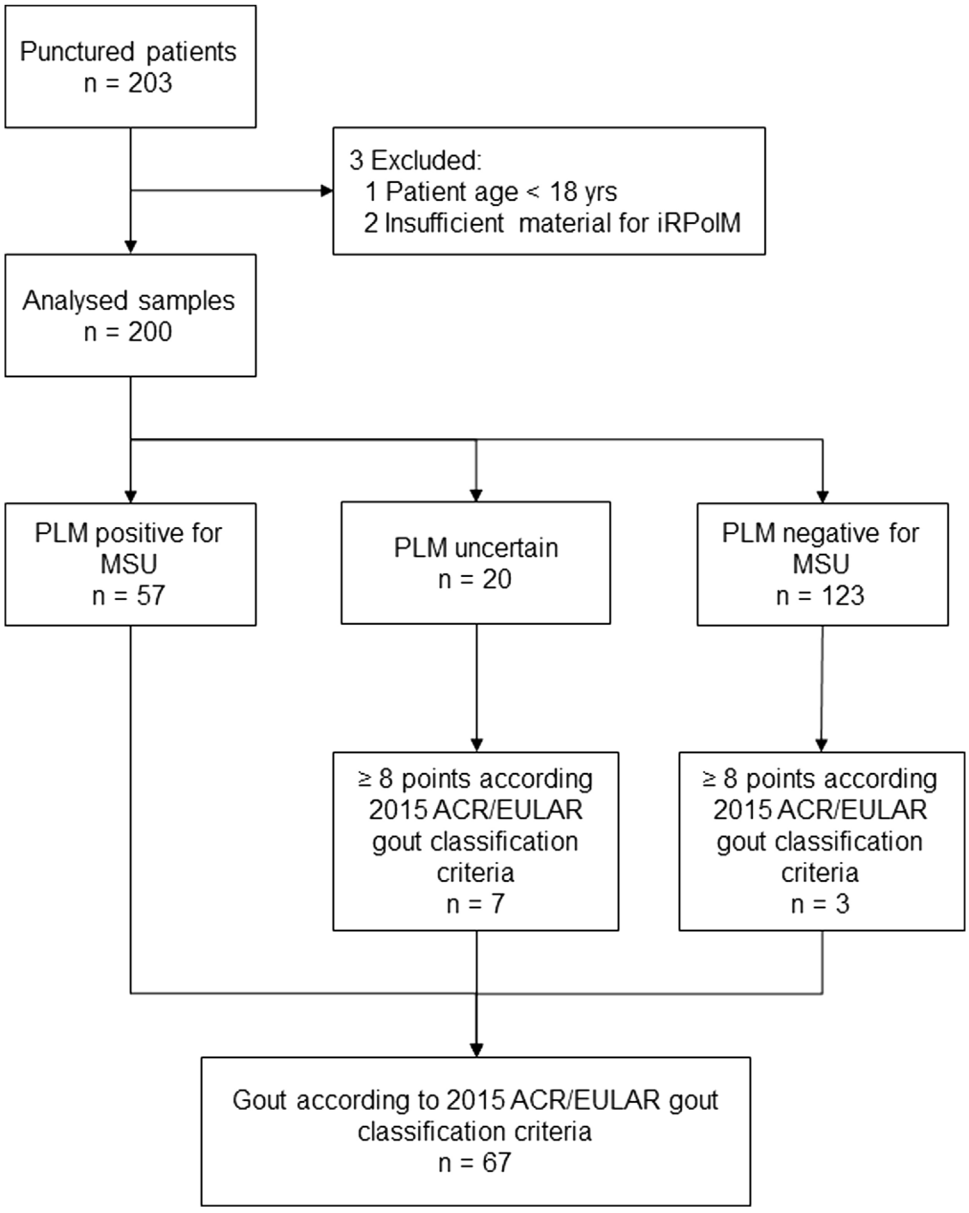

Fig. 1. Schematic overview of the flow of participants. Polarized light microscopy (PLM) analysis by rheumatologist or physician assistant. PLM uncertain samples were samples with an uncertain outcome in microscopy due to few crystals or presence of possible artefacts.

indicates a weak agreement, $0.60 < \kappa < 0.79$ indicates a moderate agreement, $0.80 < \kappa < 0.89$ indicates a strong agreement and $\kappa > 0.90$ indicates a near perfect agreement [24]. All calculations were performed with MATLAB R2020a (MathWorks corporation, Massachusetts, USA).

2.4. Role of funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

3. Results

A total of 203 consecutive patient synovial fluid samples were delivered for iRPolM analysis in this study between April 2022 and December 2022. Three samples were excluded, one because the patient was not of adult age thus not meeting inclusion criteria, and two because there was not enough sample left for additional analysis. In total, 200 synovial fluid samples were analysed. iRPolM analysis was on average performed within 1 day after arthrocentesis (SD ± 1.7).

The mean age of the patients included was 64.7 (SD ± 15.0), and 129 patients were male subjects (64.5%). There was no data on race or ethnicity collected. Of the 200 analysed samples, 32 were retrieved from first metatarsophalangeal joints, 24 from ankle joints, 87 from knee joints, 16 from wrists, and 41 from other joints, including fingers, hips, and shoulders. A total of 67 patients were classified as gout according to the 2015 ACR/EULAR gout classification criteria; 57 were positive for MSU according to PLM, and an additional 10 were negative for MSU but had a score of eight points or more. In 20 patients, PLM was uncertain. From the PLM-positive group, 36 had a gout classification score of eight points or higher. The control group included 28 patients with calcium pyrophosphate-associated arthritis, 11 patients with osteoarthritis, 25 patients with rheumatoid arthritis, four patients with bacterial arthritis, and 65 patients with an unspecified arthritic disease. The

Table 1
Baseline patient characteristics.

	Total	Positive for 2015 ACR/EULAR Gout classification criteria	Negative for 2015 ACR/EULAR Gout classification criteria
Patient count	200	67 (33.5%)	133 (66.5%)
Clinical diagnosis			
Gout	67 (33.5%)	67 (100%)	
CPPD	28 (14.0)		28 (21.5%)
Osteoarthritis	11 (5.5%)		11 (8.3%)
Rheumatoid arthritis	25 (12.5%)		25 (18.8%)
Septic arthritis	4 (2.0%)		4 (3.0%)
Undefined	65 (32.5%)		65 (48.9%)
Sex			
Male	129 (64.5%)	52 (77.6%)	77 (57.9%)
Female	71 (35.5%)	15 (22.4%)	56 (42.1%)
Age (years)			
Mean age (SD)	64.7 (SD ± 15.0)	66.3 (SD ± 14.8)	63.9 (SD ± 15.0)
Analysed joint or bursa			
MTP1[a]	32 (16.0%)	25 (37.3%)	7 (5.3%)
Ankle	24 (12.0%)	9 (13.4%)	15 (11.3%)
Knee	87 (43.5%)	11 (16.4%)	76 (57.1%)
Wrist	16 (8.0%)	2 (3.0%)	14 (10.5%)
Other[b]	41 (20.5%)	20 (29.8%)	21 (15.8%)
Microscopy confirmed MSU			
Present	57 (28.5%)	57 (85.1%)	
Uncertain	20 (10.0%)	7 (10.4%)	13 (9.8%)
Not present	123 (61.5%)	3 (4.5)	120 (90.2%)
2015 EULAR/ACR Gout classification score[c]			
<4	125 (62.5%)	5 (7.5%)	120 (90.2%)
4–7	34 (17.0%)	21 (31.3%)	13 (9.8%)
8–12	26 (13.0%)	26 (38.9%)	
12+	15 (7.5%)	15 (22.3%)	
Serum urate[d]			
Unknown	45 (22.5%)		45 (33.8%)
<250 μmol/L	18 (9.0%)	1 (1.5%)	17 (12.8%)
250–360 μmol/L	48 (24.0%)	8 (11.9%)	40 (30.1%)
370–480 μmol/L	48 (24.0%)	28 (41.8%)	20 (15.0%)
490–600 μmol/L	31 (15.5%)	21 (31.3%)	10 (7.5%)
>600 μmol/L	10 (5.0%)	9 (13.4%)	1 (0.8%)

Data are average (standard deviation) or *n* (%).
[a] MTP1 = first metatarsophalangeal joint.
[b] Other joints include hand, elbow, hip, shoulder, and bursae.
[c] According to 2015 ACR/EULAR Gout classification criteria, a patient is considered positive for gout if synovial fluid analysis is positive for the presence of MSU crystals or if 8 or more points can be awarded.
[d] Highest ever recorded value.

Table 2
Test results of iRPolM spectroscopy against the 2015 ACR/EULAR gout classification criteria, which includes synovial fluid analysis with PLM.

	Gout according to 2015 ACR/EULAR Gout classification criteria	Non-gout according to 2015 ACR/EULAR Gout classification criteria
MSU positive according to iRPolM spectroscopy	52	3
MSU negative according to iRPolM spectroscopy	15	130
iRPolM performance measures against 2015 ACR/EULAR classification criteria		
Sensitivity	77.6% (95% CI: 65.8–86.9)	
Specificity	97.7% (95% CI: 93.5–99.5)	
Positive predictive value	94.5% (95% CI: 84.9–98.2)	
Negative predictive value	89.7% (95% CI: 84.7–93.1)	
Accuracy	91.0% (95% CI: 86.15–94.6)	
Positive likelihood ratio	34.4 (95% CI: 11.16–106)	
Negative likelihood ratio	0.23 (95% CI: 0.15–0.36)	

iRPolM: integrated with an ordinary polarized light microscope; PLM: polarized light microscopy; MSU: monosodium urate. Between brackets: 95% CI = 95% confidence interval.

flow of participants and patient characteristics can be found in Fig. 1 and Table 1.

A total of 55 patients were positive for the presence of MSU according to iRPolM (Table 2): 52 were positive and three were negative according to the 2015 ACR/EULAR gout classification criteria. A total of 15 samples were classified as gout according to 2015 ACR/EULAR gout classification criteria were negative for the presence of MSU according to iRPolM. In total, 130 patients were non-gout and negative for MSU in iRPolM. Distributions of 2015 ACR/EULAR gout classification scores are given in Figure S1.

There were 57 patients in which MSU was identified by PLM, and 20 patients in which PLM was uncertain. iRPolM identified MSU in 55 patients (Table 3). There were five patient samples in which PLM was positive but iRPolM could not identify MSU. Of these five

Table 3
Test results of iRPolM spectroscopy against MSU identification in synovial fluid samples with PLM by rheumatologist.

	MSU positive according to PLM	MSU negative according to PLM	Uncertain
MSU positive according to iRPolM spectroscopy	52	3	0
MSU negative according to iRPolM spectroscopy	5	120	20
iRPolM performance measures against classification with PLM			
Sensitivity	91.2% (95% CI: 80.7–97.1)		
Specificity	97.6% (95% CI: 93.0–99.5)		
Positive predictive value	94.6% (95% CI: 85.0–98.2)		
Negative predictive value	96.0% (95% CI: 91.2–98.2)		
Accuracy	95.6% (95% CI: 91.4–98.2)		
Positive likelihood ratio	37.4 (95% CI: 12.2–114)		
Negative likelihood ratio	0.09 (95% CI: 0.04–0.21)		
Cohen's Kappa	0.90		

iRPolM: integrated with an ordinary polarized light microscope; MSU: monosodium urate; PLM: polarized light microscopy. PLM uncertain samples were samples with an uncertain outcome in microscopy due to few crystals or presence of possible artefacts. Between brackets: 95% CI = 95% confidence interval.

patients, one had 2015 ACR/EULAR gout classification criteria score above eight points, and four were negative for gout according to the classification criteria. Of the three patients positive with iRPolM but negative according to PLM, none were sufficient according to 2015 ACR/EULAR gout classification criteria. In 20 samples, the rheumatologist was uncertain of the crystal identification. iRPolM did not identify MSU in any of those. There were no uncertain outcomes in terms of MSU presence with iRPolM; the typical spectrum of MSU crystals is either measured or it is not.

Possible mistakes in subjective PLM analysis can be caused by artifacts. Glass shavings and slivers from the production of microscope slides can present as negative-birefringent needles i.e. MSU look-alikes, as an example shows in Fig. 2. With the application of Raman spectroscopy, the distinction can easily be made. MSU is recognized with the Raman scatter bands at 488, 594, 630, 785, 870, 1005, 1058, 1125, 1206 cm^{-1}, and the 1360–1442 cm^{-1} region. Full analysis time took 5–15 minutes per patient, dependent on the number of detectable crystals. Samples with high crystal counts are analysed faster, the limiting factor in analysis time is crystal localisation. Due to the non-interventional nature of this study, there are no adverse effects to be reported.

4. Discussion

In this study, it was demonstrated that iRPolM can diagnose gout with a sensitivity of 77.6% (95% CI: 65.8–86.9) and a specificity of 97.7% (95% CI: 93.5–99.5) with respect to the 2015 ACR/EULAR Gout classification criteria set. A direct comparison with polarization microscopy demonstrates high performance results, with a sensitivity of 91.2% (95% CI: 80.7–97.1) and a specificity of 97.6% (95% CI: 93.0–99.5). There is a large similarity in outcome between iRPoLM and regular PLM, with a Cohen's Kappa of 0.90. The primary advantages of the iRPolM over PLM are increased objectivity and very high (chemical) specificity. These results show that iRPolM can be used as a diagnostic test with similar performance regarding sensitivity as conventional PLM. With the integration of Raman spectroscopy, physicians can easily and objectively discriminate between MSU and glass shavings, contamination artefacts, and microcrystals or deposits of any other nature. As any patient with PLM verified MSU needles is diagnosed with gout, the specificity of PLM for gout is per definition 100%, while this is hard to verify [1,19]. The known imperfect interrater agreement of PLM raises the question whether the specificity of PLM for MSU identification is indeed 100% [6]. A Raman spectrum, however, is a unique characteristic of the chemical composition of the analyte and therefore a 100% specific identifier of the crystal, even in cases with a low a-priori likelihood. This high specificity, together with strong predictive values, accuracy and likelihood ratios prove the viability of iRPolM as a tool for clinicians to diagnose gout.

There were eight cases of disagreement between PLM and iRPolM. In the current method with PLM defined as gold standard, these are thus defined as false negatives or false positives for iRPoLM. Therefore, these cases negatively impact the calculated diagnostic performance values of iRPolM. Furthermore, 15 patients with gout were negative for MSU according to Raman spectroscopy. Not all patients have optically detectable MSU needles in their synovial fluid samples, which is a limitation of the diagnostic sensitivity of both PLM and iRPolM. In the subset of gout samples which are MSU positive according to PLM, sensitivity is > 90%. Limits to the sensitivity of iRPolM might include small particle size, low crystal counts or high interference from background signal, such as haemoglobin in samples with high erythrocyte count. These technical issues should be addressed in further developments of the technology.

Strong points of this study include: no pre-selection on patient samples for inclusion and investigating the performance of iRpolM in both the complete set of gout patients and the subset of gout patients positive for MSU with PLM. This reduces bias and both the diagnostic performance (how well can gout be diagnosed) and analytical performance (how well can MSU be identified) could be estimated. This study also had limitations. For 45 patients in the non-gout cohort, no data on serum urate was available, and no radiographic imaging was performed, because of higher clinical suspicion on an alternative arthritic disease. This hardly influences the fulfilment of the 2015 ACR/EULAR gout classification criteria, as most (57 of 67) gout patients were scored based on MSU crystals identified with PLM. Only a single observer analysed the samples with polarization microscopy, which may increase the uncertainty of the outcome. Clinical presentation was known to the rheumatologist prior to PLM analysis, as is the custom in routine clinical practice. This could lead to a possible confirmation bias in PLM and therefore an artificially high sensitivity of PLM. As the outcome of the reference test is based on these results, the sensitivity and NPV of iRPolM for the identification of MSU might be underestimated. Raman spectra are chemical fingerprints; thus confirmation bias is not present in any Raman spectroscopy-based method. Limitations to generalisability include the fact that only clinicians from one hospital with a special dedication to PLM reviewed the samples and the outcomes might not represent how an average rheumatologist would have performed.

Although not reported here, Raman spectroscopy can also be applied for the identification of calcium pyrophosphate (CPP) crystals in calcium pyrophosphate-associated arthritis (CPPD) [15,17]. We here refrain from presenting data on CPP because of the current lack of a standardized method for the classification of CPPD and a lower prevalence of CPP crystals in synovial fluid samples. Diagnostic accuracy data of iRPolM for identification of CPP might be expected in future work, as criterion sets are under development

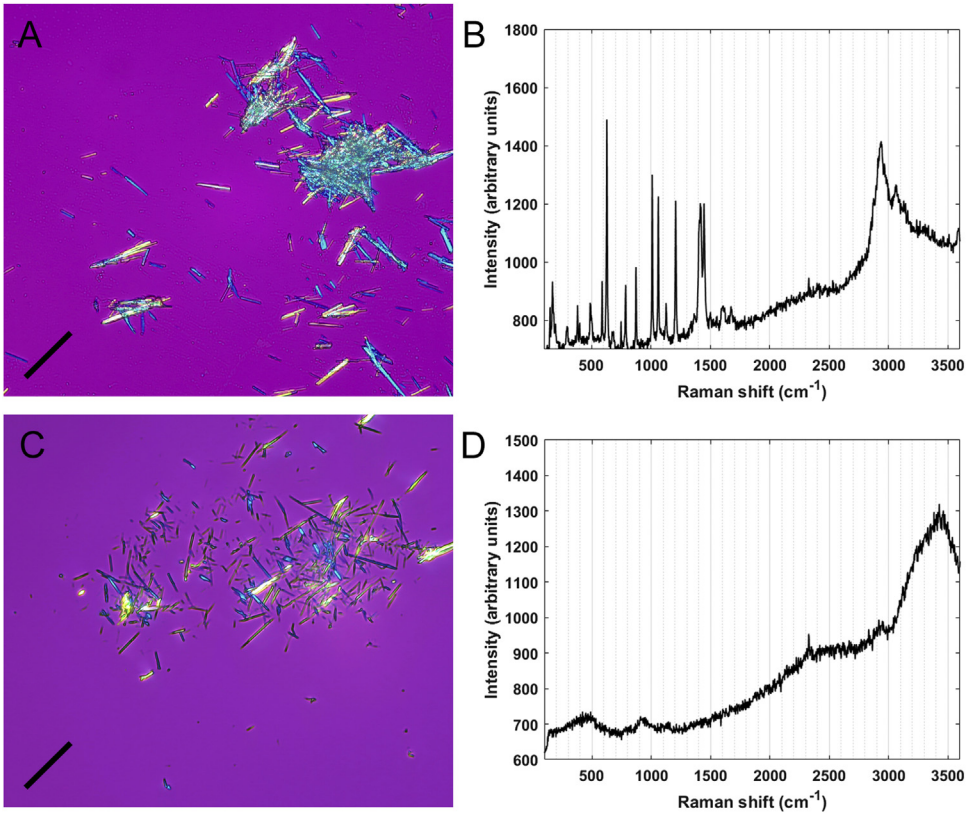

Fig. 2. A. Compensated polarized light microscopy image from monosodium urate (MSU) crystals of a patient with tophaceous gout (Zeis Axiolab 5, 63×/0.85N.A. objective). Black line shows slow axis direction. B. Raman spectrum of MSU measured with an integrated with an ordinary polarized light microscope (iRPolM) Raman Spectroscope. C. Compensated polarized light microscopy image of glass splinters (Zeis Axiolab 5, 63×/0.85N.A. objective). Black line shows slow axis direction. D. Raman spectrum of glass splinters measured with an iRPolM Raman Spectroscope.

[25]. Furthermore, Raman spectroscopy can be used to identify other (calcium containing) crystals, such as hydroxyapatite, calcium oxalate and calcium carbonate [17].

We here demonstrated that Raman spectroscopy is viable as a rapid in-vitro diagnostic tool for acute arthritic diseases suspected of gout, and clinical adaptation should be considered. Superiority of Raman spectroscopic techniques over PLM should be proven in further prospective studies for several crystallopathies. As transdermal Raman spectroscopy is technically feasible [14], Raman spectroscopy-based technologies might eventually fully eliminate the necessity for arthrocentesis in the near future.

Contributions

TN: conceptualisation, data curation, formal analysis, software, investigation, visualisation, methodology, writing (original draft), project administration. TG, ME, ACC: resources, formal analysis, investigation, writing (review and editing). MJ: conceptualisation, funding acquisition, validation, investigation, methodology, writing (review and editing). CO: conceptualisation, funding acquisition, validation, investigation, methodology, supervision, writing (review and editing). TLJ: resources, conceptualisation, funding acquisition, validation, investigation, methodology, supervision, writing (review and editing).

Data sharing

Scores on individual elements of the 2015 ACR/EULAR classification criteria and the outcome of Raman analysis for individual patients are available on the 4TU.Researchdata repository: https://data.4tu.nl/portal. The full study protocol is available on our institute website: utwente.nl/MCBP.

Disclosure of interest

Cees Otto: CEO of Hybriscan Technologies B.V., a company that produces and sells Raman spectrometer devices, including H-iRPolM, which was used for this study.

Matthijs Janssen, Tim L. Jansen: Owners of Human Crystal Research B.V., a company interested in the development of tools used for the clinical identification of synovial crystals.

The other authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data (figure S1) associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jbspin.2023.105611.

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