Identifying tophaceous gout in foot ulcers using ulcer debris microscopy in Type 2 diabetes

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ABSTRACT

Summary

Gout is frequently underdiagnosed in patients with diabetes. As a chronic disease characterised by urate deposition, gout can lead to the formation of tophi in the feet, which may ulcerate. However, the prevalence of tophaceous gout in patients with diabetes and foot ulcers has not been previously studied.

This study explored the feasibility of sampling foot ulcer debris for polarised light microscopy to detect birefringent urate crystals and identify cases of gout in patients with diabetes. Among 36 ulcer debris samples examined, urate crystals were identified in five cases (14%) strongly suggesting previously unrecognised gout. Radiographic findings further supported tophaceous gout as the primary cause of these foot ulcers.

These findings indicate that unrecognised tophaceous gout may be relatively common among patients with Type 2 diabetes and foot ulcers. However, selection bias may have led to an overestimation of prevalence, while insufficient or contaminated samples may have resulted in an underestimation. Further refinement of sampling and examination techniques—ideally supplemented by imaging prior to ulcer treatment —is needed to improve the detection of all cases with urate crystals and to ensure that negative findings truly reflect the absence of gout rather than technical limitations.

Keywords diabetes, gout, foot ulcer, amputations.

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KEY MESSAGES

- **Why did we undertake this study**? Tophaceous gout often goes unrecognised, potentially leading to foot ulcers. We aimed to determine whether sampling foot ulcer debris for urate crystals could confirm a diagnosis of gout in patients with foot ulcer and diabetes.
- **What did we find?** Among 36 patients, we identified urate crystals in five (14%) cases, strongly suggesting previously unrecognised gout. However, selection bias may have led to an overestimation of prevalence, while insufficient and contaminated samples could have resulted in an underestimation of the true prevalence of gout.
- **What are the implications of our findings?** Our findings indicate that microscopic examination of foot ulcer debris may be an assessable way to diagnose gout. Further refinement of sampling and examination techniques—ideally supplemented by imaging—is needed to improve the detection of all cases with urate crystals and to ensure that negative findings truly reflect the absence of gout rather than technical limitations.

INTRODUCTION

Diabetes is a prevalent disease, affecting ~6% of the global population.[1] About 20% of individuals with diabetes develop foot ulcers.[2] Foot ulcers are the primary cause of nontraumatic foot amputations and are associated with a five year mortality rate >50%.[3]

Gout is similarly common, with a prevalence ranging from 2% to 3% in Europe.[4-6] It occurs more frequently in people with reduced kidney function, hypertension, obesity, and heart disease and in those using diuretics—all common in people with diabetes.[7-9] While the prevalence of diabetes among patients with gout is well-documented, with estimates ranging from 10% to 37% the prevalence of gout among patients with diabetes remains less studied.[10,11] The few available studies suggest a prevalence of 8% to 22%.[12,13] These figures may be underestimated, as population studies indicate that more than 30% of cases of both gout and diabetes go undiagnosed.[1,14]

Gout often leads to the formation of urate deposits, known as tophi, in the feet, which may ulcerate and even masquerade as diabetic foot ulcers, as reported in a few case series.[15-18] Left

untreated, gout can perpetuate urate deposition, hindering ulcer healing and leading to new or recurrent foot ulcers with an increased risk for amputation.[13,15,19]

Since 2016, the European Alliance of Associations for Rheumatology has recommended a treat-to-target strategy for every patient with gout, aiming to maintain the serum urate (s-urate) level at <0.36mmol/L (equivalent to s-urate <6mg/dL), and for tophaceous gout, s-urate level <0.30mmol/L (<5mg/dL).[20-22]

Urate lowering therapy (ULT) is an effective, safe, and affordable treatment option that can prevent and dissolve tophi.[23] However, <40% of patients with gout receive sufficient ULT to reach and maintain target s-urate levels as recommended.[8,10,11] Patients with diabetes are expected to have more frequent contact for routine diabetes care, which might imply higher awareness among staff of the recommended treatment for common comorbidities, such as gout.[24] However, a recent Danish cohort study found that only 45% of patients with both diabetes and tophaceous gout received the recommended ULT even after receiving a hospital diagnosis of gout.[25] Diagnosing gout can be challenging, as it is often overlooked or insufficiently investigated.[14,26] The gold standard for diagnosis is the identification of urate crystals through microscopy of joint fluid or tophaceous material which for practical and technical reasons is rarely performed in routine clinical practice. Examination of ulcer debris during routine foot ulcer care might represent an alternative and easier assessable way to detect urate crystals.[27]

The aim of this study was to determine whether debris samples from foot ulcers in patients with diabetes, when examined using polarised light microscopy, could indicate previously unrecognised tophaceous gout.

METHODS

The Rheumatology Outpatient Clinic at North Denmark Regional Hospital serves as the sole provider of microscopy services in the area, utilising polarised light to detect needle-shaped birefringent urate crystals for the confirmation of gout (serving an estimated population of 190,000). Traditionally, only joint fluid or tophaceous material was analysed, but starting in March 2024, this service was expanded to include the examination of debris from foot ulcers. These samples were collected from March 1 to December 31, 2024, from patients referred to either the hospital's multidisciplinary foot ulcer diabetes outpatient clinic (MDT-Clinic) or the hospital's other units, all served by the same five ulcer nurses, who oversee nearly all foot ulcer patients referred to the hospital.

Staff training and additional procedures

The MDT-Clinic staff received brief targeted training to increase awareness of gout, emphasising that tophi could be the first manifestation of the disease. S-urate measurement was incorporated into routine diabetes assessments.

Various methods for ulcer debris sampling were tested, and two standard sampling methods were found practical and used in the study, a direct print of the wet wound surface on the slide and ulcer debris transferred by a plastic brush or swab to the slide. Cotton swabs were avoided as they could cause birefringent contamination. Additionally, techniques for slide preparation, microscopy, photo documentation, sample transportation, and referral to the rheumatology clinic were evaluated.

All patients with a foot ulcer routinely undergo radiographic imaging of the affected foot, and often both feet, primarily to assess for infection. Dual-energy computed tomography (DECT) was not used in standard ulcer care during this study. However, in patients with urate crystals detected in ulcer debris, radiographs were additionally reviewed by a study radiologist (AGJ), and when possible, a DECT scan was performed to assess the extent and volume of residual urate crystal deposits after ulcer debridement. Clinical photos were available only for patients enrolled in the study and were used to describe the location of the ulcer. This study reports the initial findings from a proof-of-concept study conducted with a small patient cohort.

Inclusion criteria and sampling process

Patients were eligible for inclusion if they had a confirmed diagnosis of diabetes and were referred to the hospital with a foot ulcer during the nine-month study period in 2024. Laboratory analyses were retrieved from the hospital's laboratory IT-system (LABKA). The Shared Medical Card (FMK-Online.dk) was checked for prescribed and redeemed urate lowering medicine at the time of first visit. Patients were enrolled in the study when ulcer debris samples were collected for microscopy by the single study ulcer nurse (TSB). Sampling methods were integrated into routine ulcer debridement to simultaneously assess the debris for the presence of urate crystals. Eligible patients whose samples could not be collected due to time constraints, technical equipment issues, and dry ulcer surfaces, as well as all patients examined by the other four ulcer nurses, were not enrolled in the study.

Microscopy and diagnosis

Polarised light microscopy was performed at the in-house rheumatology clinic, with samples double-checked by two investigators to confirm the presence of urate crystals. When crystals were detected, patients were referred for clinical examination by a rheumatologist to confirm the diagnosis of tophaceous gout and initiate appropriate treatment.

Statistics

Descriptive statistics for the categorical variables were performed by computing the frequencies (percentages) in each category. Categorical data were compared using the chi-square test or Fisher's exact test (as appropriate), and continuous variables were assessed via the Mann-Whitney test.

Ethics

The study was reviewed by the North Denmark Region Committee on Health Research Ethics, which determined that it qualified as a quality improvement project utilising existing procedures and indications and therefore did not require specific approval (2-1-02-1167-24). Clinical photos were taken with the patients' consent for de-identified use.

RESULTS

During the nine-month study period, 143 eligible unique patients with diabetes were referred to the hospital because of a foot ulcer. Of those patients, 13 (9%) were in urate lowering treatment when referred to the hospital and 10 (78%) had s-urate levels 0.38–0.53mmol/l, thus exceeding recommended target s-urate.

Eighty-nine patients were examined by non-study ulcer nurses and 54 patients by the study nurse who successfully sampled ulcer debris in 36 patients who were enrolled in the study. Characteristics of all 143 eligible patients with enrolment or non-enrolment status are shown in Table 1. There was a tendency towards higher age, higher serum urate levels and reduced kidney function in the enrolled patients.

In 21 of the 36 enrolled patients, the ulcerations were located on the non-weight-bearing aspect of the foot, in 13 of them located on the first or second toe. Fifteen patients had ulcers on the weight-bearing aspect of the foot, of which 10 were located on the first or second toe.

Five of the 36 patients 5(14%) were identified with previously unrecognised tophaceous gout as the underlying cause of the foot ulcers based on microscopy findings (Table 2). Their ulcerations with detected urate crystals were located on the dorsal and medial side of the first toes or on the dorsal side of the second toes (without claw deformity). Baseline characteristics of the five confirmed cases are summarised in Table 2. Two patients reported symptoms recognised as flares and three patients had unclear symptoms and walking problems. Radiological changes typical of gout were observed in all five patients, with one case showing such changes as early as 12 years before the definitive diagnosis (Figures 1–5). Additional DECT scans were performed in two of the five patients and showed significant urate deposits (Figures 2 and 5).

All five patients initiated treatment with allopurinol and reached serum urate levels <0.30 mmol/l within three months. Representative photographs of the foot ulcers, along with corresponding radiological findings, are shown in Figures 1–5. All patients had characteristic radiographic intermediate or late stage gout changes in the form of calcification in the soft tissue, intraosseous or intracortical erosions, erosions with overhanging margins, coarse soft tissue calcifications and/or well demarcated periarticular tophi, in one patient (Case 4) with concomitant degenerative changes. Signs of infectious arthritis or osteitis in the form of osteolytic destruction and soft tissue swelling without increased density compared to normal soft tissue areas and changes characteristic of rheumatoid arthritis and psoriatic arthritis were not seen. Ulcer debris cultures were obtained from four of the five patients with urate crystals. The cultures did not indicate significant infections. In Case 2, a few colonies of *S. lugdunensis* were detected and treated with dicloxacillin. The ulcer without a culture, Case 5, healed after drainage without antibiotic treatment.

The 31 enrolled patients in whom urate crystals were neither detected nor suspected were not assessed clinically for gout-related aspects, but in 15 of them various types of contamination affected the ulcer debris quality, rendering the microscopy results unreliable for definitively ruling out urate crystal-positive ulcers.

DISCUSSION

In a hospital setting that treats patients with diabetes and foot ulcers, brief, targeted training of ulcer nurses to increase awareness of gout—combined with s-urate level measurement and foot ulcer debris examination—led to the identification of previously unrecognised gout as the likely underlying cause in 14% of examined patients. The diagnosis of tophaceous gout as the primary cause of these foot ulcers was strongly supported by radiographic findings, which revealed typical gouty erosions and urate deposits.

Radiography demonstrates a high specificity of 93% but a low sensitivity of 31% for detecting changes associated with gout.[28] The low sensitivity is partly due to a latent period of 5–10 years between the first clinical symptom and the appearance of characteristic early radiographic signs, such as a striated periosteal reaction with a lace-like pattern. This pattern is not observed in infectious arthritis or osteitis.[29] The negative findings in the cultures further support tophaceous gout, rather than bacterial infection, as the underlying cause of the foot ulcers.

Foot ulcers in patients with diabetes alone are more commonly located on weight-bearing areas of the foot and on

Table 1. Baseline status. Enrolled patients with ulcer debris sampled compared with eligible, but not enrolled, patients with diabetes and a foot ulcer but with no ulcer debris sampled. eGFR= estimated Glomerular Filtration Rate ml/min/1.73 m^2. ULT= urate lowering therapy. SD= standard deviation. IQR = Interquartile range.

Variable	All eligible n=143	Not enrolled n=107	Enrolled n=36	P-value
Age years Median (IQR)	68 (60–77)	67 (59–76)	71 (61–79)	0.09
Males	110	77%	78%	0.88
S-urate mmol/l Mean ± SD (5) Not measured	 0.39 ± 0.13 11	 0.39 ± 0.14 9	 0.43 ± 0.13 2	0.14
S-urate ≥ 0.36 mmol/l n% Not measured	 79% 11	 56% 9	 71% 2	0.14
eGFR ml/min Mean ± SD	75 ± 27	78 ± 27	64 ± 26	<0.01
eGFR <60 ml/min	42	24%	44%	0.02
HbA1c mmol/mol Mean ± SD	60 ± 22	61 ± 22	57 ± 23	0.35
HbA1c ≥48 mmol/mol	91	66%	56%	0.24
Ongoing ULT n (%)	13	8%	11%	0.63
S-urate ≥0.36 mmol/l for patients in ULT	10	78%	75%	-

the dorsal side of toes with claw deformities.[30] The type of foot ulcers observed in our study also occurs in patients with gout, but without diabetes, supporting the idea that gout—rather than diabetes—is the primarily underlying cause of these ulcers.[15]

Our findings align with previous studies suggesting that patients with gout can remain undiagnosed and untreated for decades, even when presenting with obvious tophi and characteristic radiological features. Notably, the widely used Gaffo criteria, which diagnose gout based on flare characteristics, have limited applicability in our study population.[31] Foot ulcers in elderly patients with diabetes often result from multiple overlapping factors, including neuropathy, vascular disease and infection. The elderly patients did not consistently recall previous gout attacks, instead describing more chronic or intermittent foot pain along with walking difficulties. Given this complexity, chronic tophaceous gout in this population requires a different diagnostic approach—one that prioritises objective findings over reliance on acute flare symptoms.

Several studies describe barriers to treatment in primary care. However, our cases of untreated gout over many years indicate that barriers also exist in secondary routine diabetes and ulcer care, particularly when there is a lack of specific awareness of unrecognised gout.[8,32] The current IWGDF (International Working Group on the Diabetic Foot) guidelines for the prevention and management of diabetes-related foot disease does not consider screening for gout, either in cases of ulceration or suspected active Charcot neuro-osteoarthropathy.[33]

The surgical treatment of tophaceous gout in the feet is less well studied and was summarised in 2016.[34]

Our study has limitations in estimating the true prevalence of tophaceous gout in patients with diabetes and foot ulcers. Among 36 patients, we identified urate crystals in 5 (14%) cases, strongly indicating previously unrecognised gout and subsequently confirmed the diagnosis of tophaceous gout after clinical examination and imaging. However, selection bias may have led to an overestimation of prevalence, while insufficient and contaminated samples could have resulted in an underestimation. These challenges may have introduced a sampling bias as indicated in Table 1, favoring patients who exhibited signs suggestive of gout. However, there is no indication that the patients examined by the study nurse differed systematically from those treated by the other four ulcer nurses. Therefore, this limitation is unlikely to have substantially inflated our finding that gout can be diagnosed in a substantial number of patients with foot ulcers.

Contamination of ulcer debris rendered the microscopy results unreliable in several of the 31 patients in whom urate crystals were not detected, potentially leading to a significant underestimation of the true prevalence of urate crystal-positive ulcers. Thus, methods for detecting gout through ulcer debris examination require further investigation and refinement to ensure feasibility for routine clinical use. Based on findings in this exploratory study we found these examination procedures warrant to be tested on a larger scale to screen a broader cohort of patients with foot ulcers and diabetes. Accurately identifying gout as a main contributor to foot ulcers in a substantial proportion of patients could

Table 2. Baseline characteristics of the five patients with urate crystals in foot ulcer debris and clinical confirmation of tophaceous gout. eGFR= estimated Glomerular Filtration Rate. ULT= urate lowering therapy. DECT=Dual energy computer tomography. NA= not assessible.

	Patients with Type 2 diabetes, foot ulcer and tophaceous gout				
Patient number	1	2	3	4	5
Age years	91	71	92	87	79
Gender	Male	Female	Male	Female	Female
Location foot ulcer	Right 1st toe	Right 1st, 2nd and 3rd toes	Right 2nd toe	Left 1st toe	Left 1st toe
Duration of foot ulcer (months)	3	4	Unknown	3	1
Previous amputations?	No	No	Yes, right 1st toe two years before	No.	No, but surgical removal of tophus
Visible tophi	Yes	Yes	Yes	Yes	Yes
Radiographic signs of gout?	Yes	Yes	Yes	Yes	Yes
DECT performed? Volume urate cm-cubed	No -	Yes 3.39	No -	No -	Yes 1.78
History of previous arthritis attacks	Yes, but last attack 40 years ago	Yes, several attacks for the past 11 years	Unclear. Foot and hand pain for 19 years	Unclear. Foot pain >20 years	Yes, several attacks for 3 years
Ulcer debris culture	No growth.	Few colonies with *S. lungdunensis*	Few colonies, not pathogenic	Few gram +ve, non pathogenic	NA
Previous ULT	Never	Never	Never	Never	Never
Hypertension	No	Yes	Yes	Yes	Yes

Figure 1. Case 1. (A) Photograph of the ulcer taken on the same day the debris was sampled for microscopy. (B) Radiographs, anterior and oblique view (the same day) show erosions (arrows) and soft tissue calcifications medially and dorsally at the first metatarsophalangeal joint (MTP 1) (open arrows).

Figure 2. Case 2. (A) Photograph taken by the patient at home on the day the tophus ruptured on the right second toe. Debris from the ulcer was sampled two weeks later. (B) Radiographs, anterior view (B1) and enlarged oblique view of the right foot (B2), show soft tissue calcifications at MTP 2 and 5 (open arrows) and erosion of the metatarsal head at MTP 5 (arrow). C: Supplementary dual energy computer tomography (DECT) shows precipitation of urate crystals as green masses at the right MTP 5 and MTP 1 bilaterally and between the right MTP 2 and MTP 3 (arrow). There were corresponding urate deposits at the left forefoot and also in the tarso-metatarsal region where there were no visible gout changes on the radiographs. The total volume of urate deposition in the scan-field was 3.39 cm-cubed.

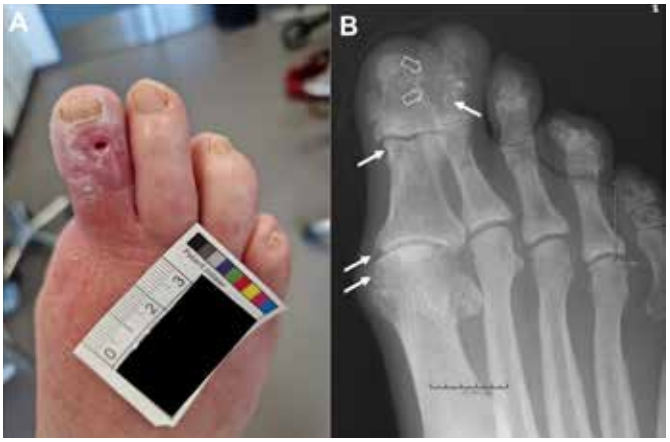

Figure 3. Case 3. (A). Photograph of the right second toe taken on the day ulcer debris was sampled. The right first toe had been amputated two years earlier. Anterior radiographs of the right foot 7 years previously show tophus formation in the soft tissues at the second distal interphalangeal joint (open arrows) with accompanying osseous destruction (arrow) in addition to characteristic erosive changes at the first metatarsophalangeal and interphalangeal joints (arrows).

Figure 4, case 4. Figure 4. Case 4. (A) Photograph of the ulcer at the left first MTP joint taken on the day of debris sampling. (B) Microscopy (10x magnification) with polarised light showing numerous needle-shaped birefringent urate crystals. Anterior radiographs of the left foot (C1) with additional magnification of the first metatarsophalangeal joint (C2) show soft tissue swelling at MTP 1 with weak condensations (open arrows) compatible with urate deposits and superficial erosions at the base of the proximal phalanx (arrows). In addition, there is hallux valgus deformation with bone apposition medially on the metatarsal head.

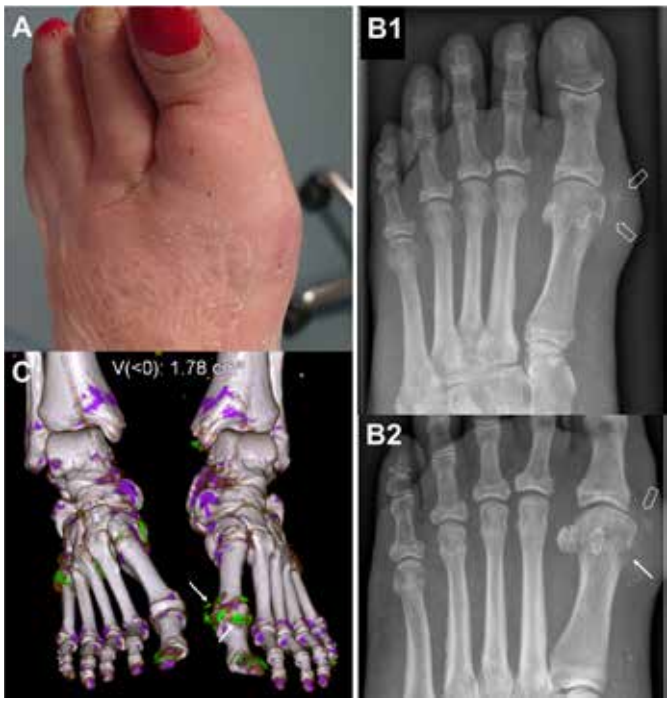

Figure 5. Case 5. (A) Photograph of a dry ulcer taken six weeks after surgical drainage of a tophus at the left first metatarsophalangeal joint. Ulcer debris for microscopy was sampled the day following the surgical drainage. (B) Radiographs, anterior view (B1) and enlarged oblique view of the left foot (B2),show soft tissue calcifications medially and dorsally at MTP 1 (open arrows) and erosion at the metatarsal head (arrow). C. Supplementary DECT two months later shows precipitation of urate crystals as green masses at the left MTP 1 (arrows) and also at the left tarsal region and medially at the left ankle in addition to the right tarso-metatarsal region. The total volume of urate deposition in the scan-field was 1.78 cm-cubed. The green deposits at the nails are due to artefacts.

support the implementation of gout screening in routine diabetes care, enhancing prevention of this common and treatable condition.[19, 24, 31]

CONCLUSION

This study explored the feasibility of sampling foot ulcer debris in patients with diabetes to detect urate crystals and confirm gout. Using this method, we successfully identified a substantial number of patients with previously unrecognised tophaceous gout. Supported by radiological findings, our assessment indicated that gout was the most likely underlying cause of their foot ulcers.

IMPLICATION FOR CLINICAL PRACTICE AND FURTHER RESEARCH

Untreated tophaceous gout may be more common than previously thought among patients with foot ulcers and diabetes. Given that effective and safe treatments for gout are available, addressing this condition could help prevent at least some foot ulcers while also improving patients' quality of life. This underscores the importance of raising awareness about unrecognised and undertreated gout and emphasises the need for proactive diagnostic measures. These include routine measurement of urate levels, careful evaluation of standard radiographs, puncture of suspected tophi or ulcer debris for microscopy, and increased use of DECT when available.

The results and methods used in our study for sampling and analysing foot ulcer debris show promise. However, further research is needed to refine these techniques and establish their reliability for integration into routine clinical practice.

Contributorship statement: CR conceived and designed the study, applied for approvement and trained the research nurses in gout care. CR and JWL oversaw development of the project database. JWL provided nurse-led gout care, and together with MLS provided suggestions for ulcer sampling, preparation and microscopy. JWL and CR did the analysis and interpretation of the clinical data. STJ provided clinical biochemistry data. PH provided input to diabetes and foot ulcer care. TSB conducted pre-study screening of patients with foot ulcers, provided ulcer care and debris sampling. AGJ critically reviewed the radiological material and provided the legends. GLN critically reviewed the manuscript and the presentation of data. All authors critically revised the work for intellectual content, approved the final version, and agreed to be accountable for the work. CR is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The study was reviewed by the North Denmark Region Committee on Health Research Ethics, which determined that it qualified as a quality improvement project utilising existing procedures and indications and therefore did not require specific approval (2-1-02-1167-24). Clinical photos were taken with the patients' consent for de-identified use.

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