

Tophaceous Gout: Quantitative Evaluation by Direct Physical Measurement

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ABSTRACT. Objective. The absence of accepted standardized methods for monitoring tophaceous gout limits the ability to track tophus progression or regression. This multicenter study assessed intra- and interrater reproducibility of a simple and direct physical measurement.

Methods. The quantitative evaluation was the area (mm^2) of each measurable tophus and was determined independently by 2 raters on 2 occasions within 10 days. Intra- and interrater reproducibilities were determined by calculating mean differences and average percentage differences (APD) in measurements of areas for the same tophus at each of 2 visits and by each rater, respectively.

Results. Fifty-two tophi were measured in 13 subjects: 22 on the hand/wrist, 16 on the elbow, and 14 on the foot/ankle. The mean (\pm SD) difference in tophus areas between visits was $-0.2 \pm 835 \text{ mm}^2$ (95% CI -162 to 162 mm^2) and the mean (\pm SD) APD was $29\% \pm 33\%$. The mean (\pm SD) APD between raters was $32\% \pm 27\%$. The largest variations in measurements were noted for elbow tophi and variations were least for well demarcated tophi on the hands.

Conclusion. This simple and reproducible method can be easily utilized in clinical trials and in practice as a measure of efficacy of urate-lowering treatment in tophaceous gout. Among factors contributing to variability in these measurements were the anatomic site of tophi and rater experience with the method. Restriction of measurements to well circumscribed hand or foot tophi could improve reliability, but major changes, as expected with effective therapy, can clearly be documented with this simple technique. (J Rheumatol 2005;32:2368–72)

Key Indexing Terms:
TOPHACEOUS GOUT

MEASUREMENT

Gout is a chronic urate crystal deposition disorder, which, if left untreated, may result in progressive disease, often characterized by joint and bone destruction from tophaceous deposits. A tophus is a collection of monosodium urate crystals surrounded by chronic mononuclear and giant cell reactions¹. Gouty tophi may be found virtually anywhere in the body but occur most commonly in the feet, hands, wrists, ears, knees, and at pressure points such as the olecranon bursa and the Achilles tendon. Tophus formation often proceeds without the symptoms of overt inflammation characteristic of acute gouty arthritis, but periarticular and intraarticular tophi may result in considerable deformity, progressive stiffness, and impaired function of affected joints.

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Hyperuricemia, defined as a serum uric acid concentration (sUA) $> 6.8 \text{ mg/dl}$, is the underlying metabolic aberration leading to urate crystal deposition in gout. There is substantial evidence to support the view that progression of gout to the potentially crippling and deforming tophaceous stage can usually be prevented by appropriately timed initiation of treatment aimed at sustained reversal of hyperuricemia (urate-lowering therapy)². There is, however, a paucity of reliable evidence that restoration of normal serum urate levels regularly results in elimination or reduction in the size of established urate deposits or prevents further progression of crystal deposition-induced tissue damage³.

Tophi have been detected and measured by physical examination and radiography and more recently, by ultrasound, computerized tomography (CT), and magnetic resonance imaging (MRI)^{4–9}. Although the imaging methods are potentially valuable in assessing tophi, their routine use is not practical in most clinical settings. The development of a reliable and serially applicable quantitative method to measure tophi would provide insight into the process of tophus formation and allow evaluation of the efficacy of urate-lowering agents in reversing the process. We determined the inter- and intrarater reproducibility of a previously described method for direct physical measurement of tophi in subjects with gout¹⁰.

MATERIALS AND METHODS

This was a multicenter study in which subjects with known gouty tophi (previously diagnosed by needle aspiration and polarized light microscopic examination) underwent tophi measurements at 2 visits separated by 5 to 10 days. Anatomical areas selected included the foot/ankle, hand/wrist or elbow, were > 10 mm in length and width, and were as nearly round as possible. Draining or acutely inflamed tophi were excluded. Multiple tophi from a single subject could be measured, provided each was distinct.

Two raters were selected at each study site. Raters independently measured tophi using a standard tape measure. Two axes along the skin at right angles to one another were identified. Using a ballpoint pen, the rater gently pressed the pen along the skin in the first axis from both sides of the tophus until the nodule obstructed pen movement. The distance between the 2 pen marks was measured over the top of the nodule and was recorded to the nearest millimeter. This procedure was repeated along the skin at a 90° angle, and measurement was repeated over the nodule along the second axis (Figures 1a and 1b, Figure 2). The area of the tophus was calcu-

lated by multiplying the 2 measures. When finished, the first rater removed all ink marks and the second rater repeated the procedure for each tophus. *Statistical analysis.* All subjects with tophus measurements obtained by the same rater at both visits were included in the assessment of intrarater reproducibility; those with tophus measurements from both raters at the same visit were included in the assessment of interrater reproducibility. The quantitative evaluation was the area (in mm²) of each measurable tophus as independently measured by 2 raters at each center.

Intrarater reproducibility was assessed by calculating the difference in area between the visits (Visit 2 area minus Visit 1 area) for the same tophus (pooling across raters) and comparing the mean difference versus zero with a one-sample paired t test. The difference in areas between the visits versus the average of the areas at both visits (pooling across raters) was plotted to assess the degree of disagreement (both error and bias), spot outliers, and examine trends in the differences between visits¹¹. The 95% confidence interval for the mean difference between visits was also calculated¹². The average percentage difference (APD) between the measured areas for each



Figure 1. Direct physical measurement of tophi using a tape measure. Using a ballpoint pen, press firmly in the direction chosen until movement is obstructed by the tophus. Repeat at right angles to the first and measure each to the nearest mm (see text).



Figure 2. Direct physical measurement of elbow tophus.

tophus was calculated to evaluate the degree of agreement between the visits. The APD between measured areas was determined for each tophus by dividing the absolute difference between each pair of areas by the average of the areas and multiplying by 100; a value of 0 indicated no difference between the measurements. Since each center utilized a distinct pair of raters, the assessment of interrater reproducibility was limited to the calculation of the mean APD between raters. The intra- and interrater reproducibility analyses were also conducted by tophus location (hand/wrist, foot/ankle, and elbow) to assess the contribution of anatomical region to variability in the overall results.

RESULTS

The majority of the 13 enrolled subjects were male ($n = 11$) and African American ($n = 7$) with a mean age of 61 years. A total of 52 tophi were measured; 22 on the hand/wrist, 16 on the elbow, and 14 on the foot/ankle. Tophi in the elbow region had a greater mean baseline area (3303 mm^2) than nodules located on the foot/ankle or hand/wrist (1174 and 735 mm^2 , respectively).

Among all measurable tophi, the mean (\pm SD) tophus areas on Visit 1 and Visit 2 were similar (1643 ± 2077 and $1643 \pm 2040 \text{ mm}^2$, respectively), and the mean difference between visits ($-0.2 \pm 835 \text{ mm}^2$) was not statistically significant ($p > 0.05$; Table 1). The 95% confidence interval for the mean difference in tophus areas between visits (Visit 2 minus Visit 1 area) was -162 to 162 mm^2 and the mean APD was $29\% \pm 33\%$.

An additional analysis revealed that the reproducibility of tophus measurements depended on the anatomical location of the tophus. The highest mean APD (35%) was noted for tophi located on the elbow, while tophi located on the foot/ankle had a mean APD of 31% and those located on the hand/wrist had a mean APD of 24%. An examination of the plot of the differences in tophus areas between visits versus the mean tophus areas showed that the measurement errors between visits were similar for tophi $< 500 \text{ mm}^2$, but increased with tophus sizes $> 500 \text{ mm}^2$ (Figure 3).

The mean (\pm SD) APD between raters was $32\% \pm 27\%$, and the APD varied by location of the tophus nodule (Table 2). Similar to the finding in the intrarater reproducibility analysis, the highest mean APD (37%) in measurements between raters was noted for tophi located on the elbow. In comparison, tophi located on the foot/ankle had a mean APD of 34%, while tophi located on the hand/wrist had a mean APD of 28%. The mean difference in areas between raters was not statistically significant at either study center and the ability to measure tophus nodules between raters depended on the tophus location.

DISCUSSION

Tophaceous gout is characterized by the presence of subcutaneous and periarticular nodules and has been reported to develop within 5 years of the onset of gout in 30% of untreated patients¹³, and to progressively involve higher proportions of patients. Studies in the 1950s noted that lowering of sUA with uricosuric agents was accompanied by observed decreases in the size of tophi¹⁴. The applicability of these observations to management of tophaceous gout, however, is limited by the small numbers of subjects studied and the dearth of quantitative data provided.

Until recently, clinicians and investigators have often documented only the presence or absence of tophi among patients with gout. In 2002, however, Perez-Ruiz, *et al* employed calipers to measure the area of a single target tophus serially in each of 63 patients undergoing treatment for tophaceous gout³. The overall mean diameter of the target tophi ranged from 5 to 61 mm, with the validity and reproducibility of the use of calipers not being addressed. Tophi in the elbow region were excluded from that study because of concern that inflammation and effusion in the olecranon bursa might interfere with accuracy in the measurement of adjacent tophi. During the 5-year study period,

Table 1. Intrarater reproducibility.

Tophi Location	Average Percentage Difference*	Difference**, mm^2	p^\dagger	95% CI for Mean Difference, mm^2
All locations				
N	104	104	0.998	-162, 162
Mean (SD)	29 (33)	-0.2 (835)		
Hand/wrist				
N	44	44	0.175	-22, 116
Mean (SD)	24 (24)	47 (227)		
Foot/ankle				
N	28	28	0.629	-222, 137
Mean (SD)	31 (36)	-43 (463)		
Elbow				
N	32	32	0.912	-544, 488
Mean (SD)	35 (40)	-28 (1432)		

* Calculated as the absolute difference of Visit 1 area and Visit 2 area divided by the average of Visit 1 area and Visit 2 area for the same tophus, pooled across raters. ** Calculated as Visit 2 area minus Visit 1 area for the same tophus, pooled across raters. † One-sample paired t test on the mean difference between visits.

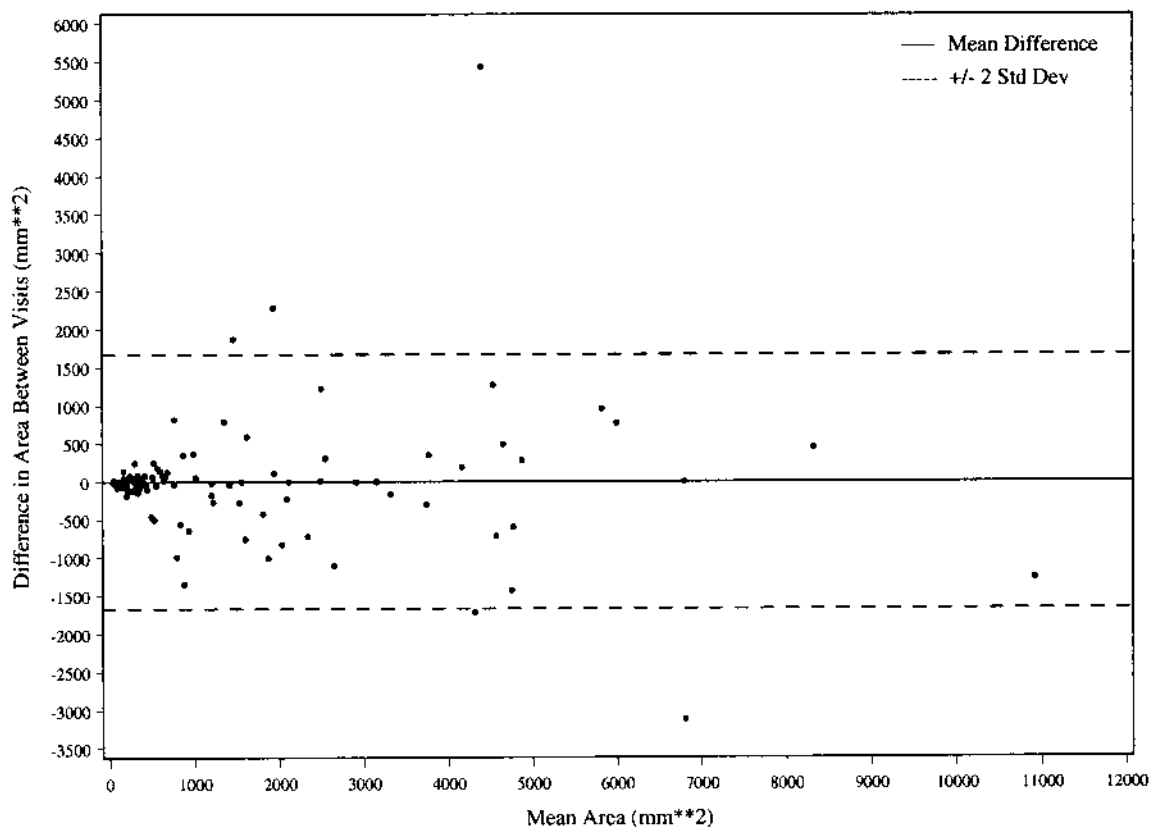


Figure 3. Plot of difference in tophus areas between visits versus mean tophus areas. Solid horizontal line represents mean difference in areas between visits; broken horizontal lines represent mean difference \pm 2 standard deviations of the difference. Mean tophus area = (Visit 1 area + Visit 2 area)/2 for each tophus measured.

all target tophi regressed completely with urate-lowering therapy aimed at achieving sUA < 6.0 mg/dl.

In our study, the reliability of a direct physical measurement for tophus area was evaluated. This method was found to be reliable and to provide a potentially useful means for clinicians and investigators to track tophus growth or

Table 2. Interrater reproducibility.

Tophi Location	Average Percentage Difference*
All locations	
N	104
Mean (SD)	32 (27)
Hand/wrist	
N	44
Mean (SD)	28 (25)
Foot/ankle	
N	28
Mean (SD)	34 (21)
Elbow	
N	32
Mean (SD)	37 (34)

* Calculated as the absolute difference of Rater 1 area and Rater 2 area divided by the average of Rater 1 area and Rater 2 area for the same tophus, pooled across visits.

regression and to monitor the efficacy of urate-lowering agents in the treatment of tophaceous gout. Although the higher mean APD and greater mean differences in measurements of elbow tophi in our study confirmed greater difficulty in tracking tophi at this site, as noted by Perez-Ruiz, *et al*³, the overall mean difference in measurements between visits was essentially zero and was not statistically significant. The observed variability in both intrarater and interrater measurements was relatively consistent with other rheumatologic measurement tools^{15,16}. No comparative studies have been done examining physical measurement with the imaging methods reported⁴⁻⁹. Focusing on well defined tophi on hands and feet could be a useful way to further improve reliability. Although we excluded inflammatory areas, elbow tophi with associated bursal effusions may have complicated measurements. We conclude that direct physical measurement of tophi, when employed serially by experienced raters, is likely to provide a simple means to evaluate efficacy of agents in the treatment of tophaceous gout that can easily be utilized in clinical research or clinical practice.

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