

Research Article

# Clinical Characteristics and Factors associated with Bone Erosion in Gout Patients with Tophi

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## Article Info

Received: May 01, 2023

Accepted: May 30, 2023

Published: Jun 06, 2023

Archived: www.jclinmedsurgery.com

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## Abstract

**Background:** A large number of urate crystals are deposited in the joint cavity for a long time, causing bone erosion and gradually forming joint skeletal muscle necrosis and joint deformity. Studies on the clinical features of tophi patients and factors associated with bone destruction have rarely aroused concern.

**Methods:** There were 135 cases of bone erosion and 75 cases of non bone erosion in tophi patients, and add up to 210 tophi patients were enrolled. The clinical characteristics were recorded and compared between the two groups. Multivariate logistic regression analysis was conducted to explore the factors associated with bone erosion.

**Results:** Compared with non bone erosion group, bone erosion group had an older age, longer disease duration of gout and tophus, higher level of serum creatinine (sCr), higher proportion of drinking history and ulceration, and lower level of glomerular filtration rate (GFR). Univariate logistic regression analysis result showed that gender, age, body mass index (BMI), gout duration, tophi duration, GFR, WBC, sCr, smoking history, drinking history, and presence of ulceration were associated with bone destruction. Multivariable logistic regression analysis result indicated that tophi duration, drinking history, ulceration and sCr were positively independently related to bone erosion.

**Conclusions:** Tophi patients with bone erosion presented different clinical characteristics. Tophi duration, drinking history, ulceration and sCr were strongly associated with bone erosion in gout patients with tophi.

**Citation:** Cji Z, Huang Y, Liang L, Guo X, Huang Q, et al. Clinical Characteristics and Factors associated with Bone Erosion in Gout Patients with Tophi. *J Clin Med Surgery*. 2023; 3(1): 1100.

## Introduction

Gout is a prevalent chronic inflammatory arthritis disease, characterized by the deposition of monosodium urate (MSU) crystals in joints, cartilage, synovial bursa, tendons or soft tissues [1]. The incidence and prevalence of gout are increasing in recent years, since the change in lifestyle and diet [2,3]. If left untreated, the frequency of acute attacks of gout increases, and deposition of urate crystals can lead to tophi and bone erosion, followed by joint damage, deformity and disability [4]. Tophi is a chronic inflammatory tissue surrounding accumulation of MSU crystals [5]. Bone erosion is a widespread complication of tophaceous gout [6]. Bone destruction in gout is closely associated with MSU crystals and the soft tissue component of tophi [7]. It is very necessary to explore other risk factors related to bone destruction in gout.

Some epidemic investigations showed that some higher risk factors for gout were found, including age, sex, alcohol consumption, diet, metabolic syndrome, hypertension, diabetes, and renal insufficiency [8,9]. The incidence of subcutaneous tophi was closely associated with duration of disease, a higher risk of cardiovascular events, renal insufficiency, kidney stones, hypertension, and higher mortality [10-12]. Mian Wu et al detected bone destruction in gout patients by using ultrasound scans and explored the affecting factors related to bone erosion, and the results showed that age, duration of gout, the number of tophi, and synovial hypertrophy were the main connected factors [13]. Since the close relationship between tophi with bone erosion, it is worthwhile to further explore the factors associated with bone destruction based on the populations of gout patients with tophi.

In our study, two groups of bone erosion and non-bone erosion constituted all gout patients with tophi recruited this time. The clinical characteristics were recorded and compared between the two groups. To investigate the factors associated with bone erosion, we used multivariate logistic regression analysis.

## Materials and methods

### Patients

A total of 210 gout patients with tophi were recruited in the study from our hospital from April 2018 to July 2021. The gout was diagnosed on the criteria of 2015 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) [14]. Gout patients with other rheumatic diseases were excluded from our study. Bone erosion was detected by X-ray examination. Gout patients with tophus were further divided into bone erosion group (n=135) and non bone erosion group (n=75). The study was approved by the EC office of Guangdong Second Provincial General Hospital (2021-KZ-131-01) and the whole process was conducted in accordance with the Declaration of Helsinki.

### Collection of clinical characteristics and laboratory data

Clinical characteristics and laboratory data, including gender, age, weight, height, smoking history, drinking history, gout duration, tophi duration, ulceration, complications, glomerular filtration rate (GFR), white blood cell (WBC), platelet (PLT), hemoglobin (HGB), alanine aminotransferase (ALT), serum uric acid (sUA), serum creatinine (sCr), C-reactive protein (CRP) and

erythrocyte sedimentation rate(ESR) were collected.

### Statistical analysis

The SPSS 23.0 software was used for database management and statistical analysis. Continuous variables were described as mean  $\pm$  standard deviation (means  $\pm$  SD), and categorical variables were described as frequencies and percentages. For continuous variables, independent sample t-tests were used to compare the differences between the groups. The chi-square test and Fisher's exact test were used for categorical variables. Univariate binary logistic regression was performed to identify statistically significant correlations between bone erosion and each potential risk factor ( $P < 0.1$ ). Variables with significant differences were defined as candidate factors for multivariate logistic regression analysis. To evaluate the independent risk factors of bone erosion, a further multivariable logistic regression model using the forward stepwise likelihood ratio method was fitted with candidate factors, with entry probability of 0.05 and removal of 0.10. Odds ratio (OR) and 95% confidence interval were calculated for the multivariate logistic model.

## Results

### Comparison of clinical characteristics between the two groups

Compared with non bone erosion group, bone erosion group had an older age, longer disease duration of gout and tophi, higher level of serum creatinine (sCr), higher proportion of drinking history and ulceration, lower level of Glomerular Filtration Rate (GFR). There were no significant differences between the two groups with regard to gender, body mass index (BMI), hypertension, diabetes, smoking history, WBC, PLT, HGB, ALT, sUA, CRP, ESR (Table 1).

### Univariate logistic regression analysis of factors associated with bone erosion

Univariate logistic regression analysis result showed that gender, age, BMI, gout duration, tophi duration, GFR, WBC, sCr, smoking history, drinking history, and presence of ulceration were associated with bone erosion (Table 2).

### Multivariable logistic regression analysis of factors associated with bone erosion

Multivariable logistic regression analysis result indicated that tophi duration (OR = 1.112, 95% CI = 1.012-1.222,  $P = 0.027$ ), drinking history (OR = 2.263, 95% CI = 1.135-4.514,  $P = 0.020$ ), ulceration (OR = 2.466, 95% CI = 1.051-5.787,  $P = 0.038$ ), sCr (OR = 1.015, 95% CI = 1.005-1.025,  $P = 0.003$ ) were positively independently associated with bone erosion (Table 3).

## Discussion

There had been many previous studies on the field of formation mechanism of tophi, clinically relevant risk factors, ulceration associated with tophaceous [15-19]. In recent years, bone destruction due to gout has attracted much attention gradually [20-23]. It is worthy of studying the relevant clinical features and risk factors of bone erosion. Our study results showed that tophi patients with bone erosion presented different clinical characteristics. Tophi duration, drinking history, ulceration and sCr were strongly associated with bone erosion in tophi patients.

**Table 1:** Comparison of clinical characteristics between the two groups.

|                                  | Bone erosion    | Non Bone erosion | P value |
|----------------------------------|-----------------|------------------|---------|
| N (male)                         | 135(132)        | 75(69)           | 0.104   |
| Age (year)                       | 52.40 ± 14.32   | 46.33 ± 13.57    | 0.001   |
| BMI (kg/m <sup>2</sup> )         | 24.66 ± 3.49    | 25.60 ± 4.21     | 0.084   |
| Gout duration (year)             | 11.80 ± 6.31    | 9.13 ± 5.47      | 0.001   |
| Tophi duration (year)            | 5.44 ± 3.86     | 3.55 ± 4.12      | <0.001  |
| GFR (ml/min/1.73m <sup>2</sup> ) | 61.61 ± 24.10   | 68.85 ± 21.98    | 0.033   |
| Hypertension, n (%)              | 39              | 39               | 0.983   |
| Diabetes, n (%)                  | 9               | 15               | 0.199   |
| Smoking history, n (%)           | 52              | 39               | 0.067   |
| Drinking history, n (%)          | 41              | 23               | 0.008   |
| Ulceration, n (%)                | 29              | 12               | 0.005   |
| WBC (10 <sup>9</sup> /mL)        | 10.79 ± 12.16   | 8.81 ± 2.72      | 0.261   |
| PLT (10 <sup>9</sup> /mL)        | 312.67 ± 112.32 | 297.48 ± 95.17   | 0.659   |
| HGB (g/L)                        | 128.04 ± 24.14  | 130.59 ± 19.23   | 0.708   |
| ALT (U/L)                        | 31.13 ± 25.07   | 32.84 ± 24.22    | 0.367   |
| sUA (umol/L)                     | 566.84 ± 115.68 | 562.19 ± 139.06  | 0.756   |
| sCr (umol/L)                     | 135.95 ± 48.94  | 117.36 ± 34.13   | 0.001   |
| CRP (mg/L)                       | 30.47 ± 38.03   | 32.26 ± 41.79    | 0.919   |
| ESR (mm/h)                       | 48.08 ± 36.50   | 47.86 ± 32.69    | 0.664   |

Abbreviation(s): BMI: Body Mass Index; GFR: Glomerular Filtration Rate; WBC: White Blood Cell; PLT: Platelet; HGB: Hemoglobin; ALT: Alanine Aminotransferase; sUA: Serum Uric Acid; sCr: Serum Creatinine; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate.

**Table 2:** Univariate logistic regression analysis of factors associated with bone erosion.

|                  | β      | OR(95%CI)           | P value |
|------------------|--------|---------------------|---------|
| N (male)         | -1.342 | 0.261 (0.063-1.077) | 0.063   |
| Age              | 0.031  | 1.031 (1.010-1.053) | 0.004   |
| BMI              | -0.067 | 0.936 (0.867-1.009) | 0.085   |
| Gout duration    | 0.081  | 1.085 (1.028-1.145) | 0.003   |
| Tophi duration   | 0.156  | 1.169 (1.062-1.288) | 0.002   |
| GFR              | -0.013 | 0.987 (0.975-0.999) | 0.035   |
| Hypertension     | -0.006 | 0.994 (0.557-1.774) | 0.983   |
| Diabetes         | -0.566 | 0.568 (0.237-1.358) | 0.203   |
| Smoking history  | 0.535  | 1.708 (0.962-3.034) | 0.068   |
| Drinking history | 0.853  | 2.346 (1.236-4.450) | 0.009   |
| Ulceration       | 1.092  | 2.979 (1.353-6.562) | 0.007   |
| WBC              | 0.08   | 1.084 (0.994-1.182) | 0.069   |
| PLT              | 0.001  | 1.001 (0.999-1.004) | 0.323   |
| HGB              | -0.005 | 0.995 (0.982-1.008) | 0.431   |
| ALT              | -0.003 | 0.997 (0.986-1.009) | 0.631   |
| sUA              | <0.001 | 1.000 (0.998-1.003) | 0.794   |
| sCr              | 0.013  | 1.013 (1.004-1.022) | 0.005   |
| CRP              | -0.001 | 0.999 (0.992-1.006) | 0.752   |
| ESR              | <0.001 | 1.000 (0.992-1.008) | 0.965   |

Note: Analysis was performed using univariate binary logistic regression. Abbreviation(s): CI: Confidence Interval; BMI: Body Mass Index; GFR: Glomerular Filtration Rate; WBC: White Blood Cell; PLT: Platelet; HGB: Hemoglobin; ALT: Alanine Aminotransferase; sUA: Serum Uric Acid; sCr: Serum Creatinine; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate

**Table 3:** Multivariable logistic regression analysis of factors associated with bone erosion.

|                  | β     | OR(95%CI)          | P value      |
|------------------|-------|--------------------|--------------|
| Tophi duration   | 0.106 | 1.112(1.012-1.222) | <b>0.027</b> |
| Drinking history | 0.817 | 2.263(1.135-4.514) | <b>0.02</b>  |
| Ulceration       | 0.903 | 2.466(1.051-5.787) | <b>0.038</b> |
| sCr              | 0.015 | 1.015(1.005-1.025) | <b>0.003</b> |

Note: Analysis was performed using multivariate binary logistic regression.

Abbreviation(s): CI: confidence interval; sCr: serum creatinine

With the sUA uncontrolled, the incidence and prevalence of bone erosion are increasing in recent years. It is very necessary to explore other risk factors related to bone destruction in gout. Mian Wu et al detected bone destruction in gout patients by using ultrasound scans and explored the factors connected with bone destruction, and the results showed that age, duration of gout, the number of tophi, and synovial hypertrophy were the main correlative factors [13]. In the present study, we further explored the factors associated with bone erosion based on the populations of gout patients with tophi. And the result showed that tophi duration, drinking history, ulceration and sCr were strongly associated with bone erosion in gout patients with tophi. It is different from the previous study [13], which can deepen our understanding of the risk factors of bone destruction.

The age was older and duration of gout was longer in bone erosion, but they were not the risk factors of bone erosion. The gender, BMI, sUA, CRP, and ESR had a close relationship with gout [24], but they showed no significant difference between the bone erosion group and none bone erosion group. McQueen et al found that erosions were not connected with bone oedema or synovitis, but strongly associated with tophi in a prospective Magnetic Resonance Imaging (MRI) study [25]. With the formation of tophi, the foreign body granulomas composed of mononuclear and multinucleated macrophages surrounding deposition of MSU would present. Increased osteoclast-mediated bone resorption and impaired osteoblast-mediated bone formation are very favorable evidences of disturbed bone remodeling in tophaceous arthritis [26]. Lee SJ et demonstrated that RANKL-expressing T cells and TRAP+ osteoclasts were present within gouty tophus tissues [27]. Regarding to prolonged tophi duration, it was correlated with the number and volume of tophi, which could aggravate bone destruction. It also suggested the importance of early detection of tophi by computed tomography, ultrasonography, and MRI. Besides, ulceration of tophi was the most forceful factor associated with bone erosion, with an OR of 2.466. It may be related to the large number of inflammatory factors caused by the ulcers. As for the relationship of drinking history and sCr with bone erosion, it may be because that alcoholism and renal impairment would lead to the uncontrolled sUA, hindering the reduction of tophi.

In addition, some limitations should be taken into account in our study. Firstly, tophi was not pathologically confirmed because of invasive investigations. Secondly, the quantity of cases was relatively small and this was a single-center study. Therefore, it is necessary to increase the sample size and conduct multicenter research to confirm the results.

### Conclusion

In conclusion, we found that there were some different clinical characteristics between bone erosion and non bone erosion

in gout patients with tophi. Tophi duration, drinking history, ulceration and sCr were independently associated with erosions in gout patients with tophi. These results indicated that reducing local urate crystal deposition, early diagnosis and treatment of tophi were essential to prevent bone erosion.

### Declarations

**Ethical approval and consent to participate:** The study was approved by the EC office of Guangdong Second Provincial General Hospital (2021-KZ-131-01) and the whole process was conducted in accordance with the Declaration of Helsinki.

**Consent for publication:** Not applicable.

**Availability of data and materials:** All data used during the study are available from the corresponding author by request.

**Competing interests:** The authors declare no conflict of interest related to this work.

**Funding:** This study was funded by Science and Technology Projects in Guangzhou, China (No. 202102020127, 202102080321).

**Authors' contributions:** Zhuyi Ji: Data curation, Methodology, Writing - original draft. Yukai Huang: Validation, Formal analysis, Writing - review & editing. Ling Liang: Software, Validation. Xin Guo: Methodology. Qidang Huang: Visualization, Investigation. Zhengping Huang: Supervision. Shuyang Chen: Visualization, Investigation. Lixin Huang: Visualization, Investigation. Shanmiao Sun: Methodology. Weiming Deng: Resources. Tianwang Li: Supervision, Funding acquisition.

**Acknowledgements:** We thank all patients and families for their participation.

### References

1. Dalbeth N, Choi HK, Joosten LAB, et al. Gout. *Nat Rev Dis Primers*. 2019; 5: 69.
2. Singh JA, Gaffo A. Gout epidemiology and comorbidities. *Semin Arthritis Rheum*. 2020; 50: S11-S16.
3. Robinson PC. Gout - An update of aetiology, genetics, co-morbidities and management. *Maturitas*. 2018; 118: 67-73.
4. Richette P, Doherty M, Pascual E, Barskova V, Becce F, et al. 2018 updated European League Against Rheumatism evidence-based recommendations for the diagnosis of gout. *Ann Rheum Dis*. 2020; 79: 31-38.
5. Dalbeth N, Pool B, Gamble GD, Smith T, Callon KE, et al. Cellular characterization of the gouty tophus: a quantitative analysis. *Arthritis Rheum*, 2010, 62(5): 1549-1556.
6. Dalbeth N, Clark B, Gregory K, Gamble G, Sheehan T, et al. Mechanisms of bone erosion in gout: a quantitative analysis using plain radiography and computed tomography. *Ann Rheum Dis*. 2009; 68: 1290-1295.
7. Sapsford M, Gamble G D, Aati O, Knight J, Horne A, et al. Relationship of bone erosion with the urate and soft tissue components of the tophus in gout: a dual energy computed tomography study. *Rheumatology (Oxford)*. 2017; 56: 129-133.
8. Saag KG, Choi H. Epidemiology, risk factors, and lifestyle modifications for gout. *Arthritis research & therapy*. 2006; 8 Suppl 1: S2.
9. Singh JA, Reddy SG, Kundukulam J. Risk factors for gout and prevention: a systematic review of the literature. *Curr Opin Rheumatol*. 2011; 23: 192-202.
10. Perez-Ruiz F, Martínez-Indart L, Carmona L, Herrero-Beites AM, Pijoan JI, et al. Tophaceous gout and high level of hyperuricaemia are both associated with increased risk of mortality in patients with gout. *Ann Rheum Dis*. 2014; 73: 177-182.
11. Ma L, Sun R, Jia Z, Zou Y, Xin Y, et al. Clinical characteristics associated with subcutaneous tophi formation in Chinese gout patients: a retrospective study. *Clin Rheumatol*. 2018; 37: 1359-1365.
12. Lu B, Lu Q, Huang B, Li C, Zheng F, et al. Risk factors of ultrasound-detected tophi in patients with gout. *Clin Rheumatol*. 2020; 39: 1953-1960.
13. Wu M, Liu F J, Chen J, Chen L, Wei C, et al. Prevalence and Factors Associated With Bone Erosion in Patients With Gout. *Arthritis Care Res (Hoboken)*. 2019; 71: 1653-1659.
14. Neogi T, Jansen T L T A, Dalbeth N, Fransen J, Schumacher HR, et al. 2015 Gout Classification Criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis & rheumatology (Hoboken, NJ)*. 2015; 67: 2557-2568.
15. Forbess LJ, Fields TR. The broad spectrum of urate crystal deposition: unusual presentations of gouty tophi. *Semin Arthritis Rheum*. 2012; 42: 146-154.
16. Schauer C, Janko C, Munoz LE, Zhao Y, Kienhöfer D, et al. Aggregated neutrophil extracellular traps limit inflammation by degrading cytokines and chemokines. *Nat Med*. 2014; 20: 511-517.
17. Rome K, Erikson K, Otene C, Sahid H, Sangster K, et al. Clinical characteristics of foot ulceration in people with chronic gout. *Int Wound J*. 2016; 13: 209-215.
18. Xu J, Lin C, Zhang P, Ying J. Risk factors for ulceration over tophi in patients with gout. *Int Wound J*. 2017; 14: 704-707.
19. Huang Z, Liu X, Liu Y, Li G, Pan X, et al. Clinical characteristics and risk factors of ulceration over tophi in patients with gout. *Int J Rheum Dis*, 2019, 22(6): 1052-1057.
20. Brook RA, Kleinman NL, Patel PA, Melkonian AK, Brizee TJ, et al. The economic burden of gout on an employed population. *Curr Med Res Opin*. 2006; 22: 1381-1389.
21. Hanly JG, Skedgel C, Sketris I, Cooke C, Linehan T, et al. Gout in the elderly--a population health study. *J Rheumatol*. 2009; 36: 822-830.
22. Singh J A, Sarkin A, Shieh M, Khanna D, Terkeltaub R, et al. Health care utilization in patients with gout. *Semin Arthritis Rheum*. 2011; 40: 501-511.
23. Khanna P P, Nuki G, Bardin T, Tausche AK, Forsythe A, et al. Tophi and frequent gout flares are associated with impairments to quality of life, productivity, and increased healthcare resource use: Results from a cross-sectional survey. *Health Qual Life Outcomes*. 2012; 10: 117.
24. Kim KY, Ralph Schumacher H, Hunsche E, Wertheimer AI, Kong SX, et al. A literature review of the epidemiology and treatment of acute gout. *Clin Ther*. 2003; 25: 1593-1617.
25. McQueen F M, Doyle A, Reeves Q, Gao A, Tsai A, et al. Bone erosions in patients with chronic gouty arthropathy are associated with tophi but not bone oedema or synovitis: new insights from a 3 T MRI study. *Rheumatology (Oxford)*. 2014; 53.
26. Ashika Chhana, Bregina Pool, Karen E Callon, Tay ML, Musson D, et al. Monosodium urate crystals reduce osteocyte viability and indirectly promote a shift in osteocyte function towards a pro-inflammatory and proresorptive state. *Arthritis Res Ther*. 2018;

27. Sung-Ji Lee, Kwang-Il Nam, Hye-Mi Jin, Cho YN, Lee SE, et al. Bone destruction by receptor activator of nuclear factor  $\kappa$ B ligand-expressing T cells in chronic gouty arthritis. *Arthritis Res Ther.* 2011; 13: R164.