

The Gouty Tophus: a Review

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Abstract The tophus is the cardinal feature of advanced gout. This review summarises recent research into the biology, impact and treatment of tophaceous gout. Microscopically, tophi are chronic foreign body granuloma-like structures containing collections of monosodium urate (MSU) crystals surrounded by inflammatory cells and connective tissue. Extracellular trap formation mediated by neutrophil interactions with MSU crystals may be a central checkpoint in tophus formation. Gouty tophi impact on many aspects of health-related quality of life. Tophi are also implicated in the development of structural joint damage and increased mortality risk in people with gout. Effective treatment of tophaceous gout requires long-term urate-lowering therapy, ideally to achieve a serum urate concentration of <5 mg/dL (300 μ mol/L). Recent advances in gout therapeutics have expanded urate-lowering therapy options for patients with severe tophaceous disease to allow faster regression of tophi, improved health-related quality of life and, potentially, improved structural outcomes.

Keywords Tophus · Tophi · Tophaceous gout · Gout · Urate · Bone · Cartilage · Tendon · Osteoblast · Osteoclast · Chondrocyte · Tenocyte · Urate-lowering therapy

Introduction

The tophus is the cardinal sign of advanced gout. The tophus represents an organised chronic foreign body granulomatous

inflammatory response to monosodium urate (MSU) crystals. These lesions typically present many years after first presentation with acute gouty arthritis, in the context of long-standing hyperuricaemia. Recent research has provided new insights into the biology, impact and treatment of the gouty tophus. In this review, we summarise these findings, focusing on key papers published in the last few years.

Search Methods

Original articles and systematic literature reviews of relevance were identified in the PubMed database using the search terms “tophus”, “tophi” and “tophaceous”. The date range was from 1 January 2011 to 31 October 2014. Only English-language, full-text papers were selected. Additional publications were selected from the reference lists of other relevant articles and from the authors’ own bibliographic files.

Composition of the Tophus

Three main zones have been identified within the tophus; the central crystalline core of MSU crystals, the surrounding highly cellular corona zone and the outer fibrovascular zone [1] (Fig. 1). The coronal and fibrovascular zones both contain numerous CD68+ macrophages and plasma cells and fewer mast cells. Neutrophils are rarely observed in the gouty tophus. T and B lymphocytes are found scattered throughout the coronal and fibrovascular zones at relatively low densities [2, 3].

Pro-inflammatory factors expressed in the gouty tophus include interleukin (IL)-1 β , IL-6, tumour necrosis factor- α (TNF- α) and myeloid-related proteins-8 and -14 [2–4]. Transforming growth factor- β (TGF- β) is also expressed in the tophus [2]. TGF- β has been shown to reduce MSU crystal-induced inflammation [5]. The expression of both pro- and

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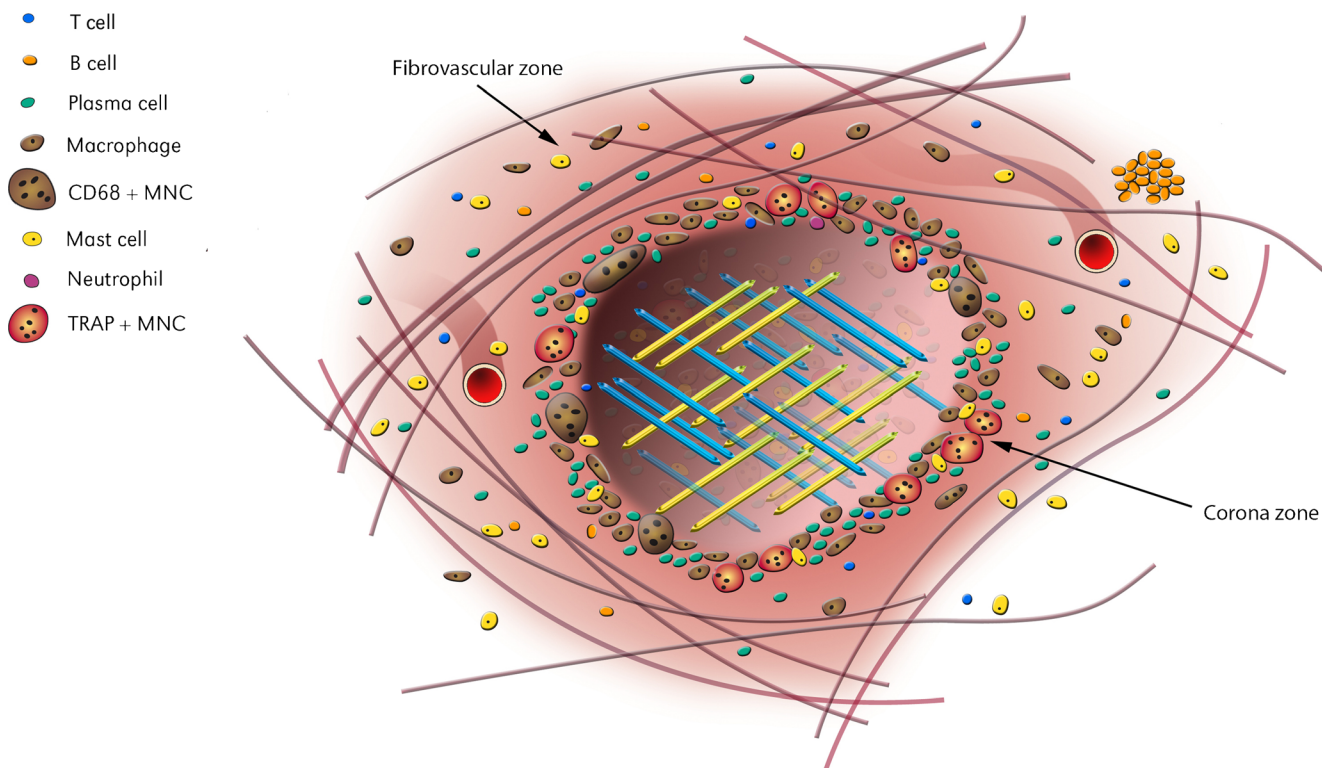


Fig. 1 A cellular model of the gouty tophus surrounding a central core of MSU crystals. The corona and fibrovascular zones within the tophus contains cells from both the innate and adaptive immune systems. *MNC*

mononuclear cells, *TRAP* tartrate-resistant acid phosphatase. Adapted from [2]

anti-inflammatory cytokines within the tophus suggests that inflammation and attempted resolution occurs within the same lesion [2].

The protein component of the tophus has recently been analysed and shown to include proteins related to adaptive immunity such as immunoglobulins and complement factors, inflammatory proteins, connective tissue and matrix proteins, apolipoproteins and histones [6•].

Formation of the Tophus

Tophi can be clinically silent for a long time with no symptoms of active inflammation, indicating that the tophus may represent a physical containment which limits MSU crystal-induced inflammation to the site of crystal deposition. Recent research has shown that neutrophil extracellular trap (NET) formation is important in this process and may contribute to tophus formation.

NETs are an extracellular method of killing pathogens employed by neutrophils and other granulocytes. NETosis (NET formation by neutrophils) can be induced by specific stimuli and results in mobilisation of granular components and ejection of intracellular material into the extracellular space following rupture of the outer cell membrane. Unfixed, hydrated NETs have a 3D cloud-like appearance [7–9]. The

gouty tophus shares some characteristics with NETs. Tophus and synovial tissue from patients with gout contain extracellular DNA which is co-localised with neutrophil granular components suggesting that NETosis has occurred [10••, 11•]. In vitro, MSU crystals rapidly induce extracellular trap formation by neutrophils, eosinophils and basophils [12••]. Synovial neutrophils and peripheral polymorphonuclear cells from patients with high serum urate levels and acute gout have enhanced NET formation in response to MSU crystals. This is partially driven by IL-1 β signalling and requires phosphoinositide 3-kinase signalling [13]. NETs may initially form in an attempt by the body to downregulate MSU crystal-induced inflammation. A recent study has shown that aggregated NETs may limit inflammation within the tophus by degrading inflammatory cytokines and chemokines [10••]. At high neutrophil densities, MSU crystals induced the formation of NET aggregates. In a mouse model, these white NET aggregates resembled small tophus-like structures and contained extracellular DNA and neutrophil granular components. An important finding of this study was that these NET aggregates actively degraded neutrophil-derived inflammatory mediators such as IL-1 β , IL-6, TNF- α and monocyte chemoattractant protein-1. In people with impaired NETosis, for example in patients with chronic granulomatous disease or in NETosis-deficient animal models, MSU crystals can lead to an exacerbated and chronic inflammation. Thus, in patients

with gout, after initial MSU crystal-induced NETosis and inflammation, the higher neutrophil density present within the gouty joint may lead to aggregated NET formation and subsequent degradation of pro-inflammatory mediators [10••]. Under normal circumstances, NETs are removed during the resolution of inflammation by DNase-1 [14]. It is possible that patients with ongoing hyperuricaemia and MSU crystal formation may have insufficient clearance of NETs, and failure of MSU crystals to dissolve in this context may lead to constant signalling for NETosis which may then lead to tophus formation.

Clinical Presentation of Tophaceous Gout

Clinically apparent tophi appear on physical examination as nodules within the subcutaneous tissues or associated with joints and tendons. The nodules have a white appearance under translucent skin (due to the appearance of MSU crystals) and may discharge white crystalline material. Aspiration of the lesion reveals MSU crystals under polarising light microscopy [15].

Typical sites for tophus deposition are well recognised including the olecranon bursa, the Achilles tendon, the first metatarsophalangeal (MTP1) joint, the ear and the finger pulps. In addition, there have been recent reports of unusual sites or presentations of tophaceous disease. This includes atypical musculoskeletal presentations causing spinal cord or nerve root compression [16–18] or involving the tarsal tunnel [19], the patellar tendon [20, 21], the second metacarpal [22] and the os trigonum [23]. Additionally, non-skeletal presentations may rarely occur, including in the bronchus, causing airways obstruction [24], the mitral valve [25], the liver [26] and the breast [27].

As described above, tophaceous gout typically occurs more than a decade after first presentation of gout in the context of untreated hyperuricaemia [28]. However, some patients present with gouty tophi early in the course of disease [29]. A recent analysis of people with gout for <10 years found that 16 % of these patients had clinical evidence of subcutaneous tophi [30]. This study identified impaired renal function as a major risk factor for the development of early tophaceous disease with a multivariate adjusted relative risk estimate of 12.0 for those with creatinine clearance <30 mL/min, compared with the reference group with creatinine clearance >90 mL/min. Another study of young Taiwanese adults with juvenile-onset gout (age of onset <20 years) also reported that eGFR was inversely related to duration of tophi in this patient group [31]. It is currently unknown whether impaired renal function contributes to early development of tophi or whether tophi have an adverse impact on renal function. High serum urate concentrations were a key risk factor for the presentation of tophaceous disease in the study of young Taiwanese adults

with juvenile-onset gout [31]. Genetic variants contributing to hyperuricaemia have also been associated with a higher risk for tophaceous disease [32, 33].

Clinical Assessment of Tophi

Many different methods have been described for the assessment of tophi [34•]. These methods include physical measurement of subcutaneous lesions; the Outcomes in Rheumatology Clinical Trials (OMERACT) group has endorsed index tophus measurement using Vernier calipers as a method for measurement in chronic gout studies [35]. Advanced imaging methods such as ultrasonography (US), magnetic resonance imaging (MRI), conventional computed tomography (CT) and dual-energy computed tomography (DECT) allow assessment of both clinically apparent and intra-articular tophi.

On ultrasonography, the tophus has been defined as “heterogeneous hyperechoic (relative to subdermal fat) aggregates with poorly defined margins with or without areas with acoustic shadowing” [36•]. In a comprehensive examination of the features of gout using ultrasonography, tophi were observed on ultrasound more frequently than was clinically apparent, with the MTP1 most commonly affected by tophus on US [36•]. Tendon involvement is frequently observed on US, particularly at the patellar tendon, quadriceps tendon and Achilles tendon [36•]. In a meta-analysis of diagnostic studies comparing imaging methods with microscopic identification of MSU crystals as the gold standard for gout diagnosis, the pooled sensitivity for US tophus was 0.65 and the pooled specificity was 0.80 [37•]. Ultrasound measurement of tophus fulfils most aspects of the OMERACT filter [35], with one observational study demonstrating sensitivity to change following urate-lowering therapy over 1 year [38].

DECT allows detection of greater urate deposition than is clinically apparent in people with tophaceous gout [39]. Although DECT has a high diagnostic accuracy for crystal-proven gout with pooled sensitivity of 0.87 and pooled specificity of 0.84 on meta-analysis [37•], it should be emphasised that the dual-energy methodology colour-codes urate crystal deposition only. DECT analysis of clinically apparent tophi with a similar physical size has shown that there is a large variation in the amount of urate crystal deposition within these lesions [35]. This observation may explain the recent report that some tophi identified at post-mortem were not apparent on ante-mortem DECT [40]. This comparison of histological and imaging findings indicated that DECT can identify ‘dense’ tophi (with at least 15–20 % urate volume in the tophus), but that tophi with lower urate volumes may not be detected on the colour-coded DECT images.

Impact of Tophaceous Gout

In a recent international survey of more than 600 people with gout, the presence of gouty tophi was associated with lower SF-36 mental component summary, physical component summary and SF-6D scores [41•]. Work disability was also significant in those with tophi, with lower work productivity, higher absenteeism and greater overall work impairment. Calculated SF-6D health utilities in those with severe gout, characterised by both tophi and recurrent flares, were lower than average health utilities of people with less severe gout and also people with other chronic rheumatic diseases.

The impact of tophaceous gout on many aspects of the patient's life was further emphasised in a qualitative study in which 25 people with gouty tophi participated in detailed interviews exploring their experience of living with gouty tophi [42]. This work identified three major themes: functional impact, psychological impact and no impact. Aspects of the functional impact theme included pain, restricted joint range of motion, joint deformity, complications such as ulceration and infection, activity limitation and participation restriction (affecting day-to-day activities, leisure activities, employment participation and family participation). The psychological theme included low self-esteem that arose from exclusion from leisure, social and work activities and embarrassment about the appearance of tophi. The final theme of no impact arose from some participants who described that tophi did not exert any impact on their lives. This study demonstrates that the experience of tophaceous disease varies widely between different individuals and that the presence of tophi can affect on not only physical function but also psychological and social function.

It seems likely that those with a greater number of tophi and those with complicated tophi causing ulceration, infection, structural damage or limitation of joint movement are more likely to report a greater impact. To date, the impact of tophi has not been quantifiable due to lack of instruments that comprehensively measure the impact of tophi on the individual. A new 20-item tophus-specific questionnaire, the Tophus Impact Questionnaire (TIQ-20), has been developed as a patient-reported outcome of tophus burden [43••]. This questionnaire was developed through qualitative interviews, cognitive testing and a Rasch analysis approach. The questionnaire captures pain, activity limitation, footwear modification, participation, psychological impact and healthcare utilisation specifically related to tophi. This questionnaire is feasible, has high face validity and construct validity, and acceptable test-retest reproducibility. An online version of the questionnaire is publically available (<http://www.fmhs.auckland.ac.nz/TIQ-20>). It is unknown whether this questionnaire is responsive to change over time and in response to therapy. Nevertheless, this tool should provide the ability to quantify the global impact of tophi on the individual with gout.

Emerging data also indicate that the presence of clinically apparent subcutaneous tophi is associated with increased mortality risk in people with gout. In a longitudinal prospective study (mean follow-up period 48 months) of a tertiary care gout clinic, the presence of tophaceous disease at the first visit was associated with a multivariate adjusted hazard ratio for death of 2.05 (95 % CI 1.29–3.28) [44•]. The majority of deaths in the cohort occurred due to cardiovascular causes. At present, it is not clear why the presence of tophi is associated with increased risk for mortality, including cardiovascular mortality.

Structural Consequences of Tophaceous Gout

Tophaceous gout has been associated with significant structural damage to tissues of the joint including cartilage, bone and tendon. A recent MRI study investigating the relationships between tophus, bone erosion, bone oedema and synovitis in 40 patients with gout found that there was a strong association between the presence of tophi and bone erosions, but not oedema or synovitis [45]. CT has shown that joints with intraosseous tophus are more likely to have features of abnormal new bone formation such as bony spurs, osteophytes, periosteal new bone formation, ankyloses and sclerosis [46]. In DECT studies, MSU crystals are frequently present in joints affected by radiographic damage in gout [47].

Cartilage damage is a late feature of gout and is typically identified on plain radiographs as joint space narrowing [48]. Analysis of MRI scans has shown that cartilage damage is predominantly focal and closely related to sites of tophus deposition [49]. In this same study, bone erosions were associated with cartilage destruction, and tophus infiltration into bone was accompanied by damage to the overlying cartilage.

Deposits of MSU crystals and tophi have been identified both adjacent to and within tendons and also at the tendon-bone interface using histology [50], ultrasonography [51], CT [36•] and DECT [52]. Tophus infiltration into tendons has also been observed during surgery [53, 54]. A recent DECT analysis in the feet of patients with tophaceous gout has demonstrated that tendon involvement in gout is much more common than previously thought. In this study, 10.8 % of the tendon/ligament sites analysed had MSU crystals present [52].

Cellular Mechanisms of Joint Damage in Gout

Previous research has implicated the osteoclast as being important in the development of bone erosion in tophaceous gout. Patients with tophi have enhanced osteoclast formation, and numerous osteoclasts are present adjacent to eroded bone in tophaceous joints [3, 55, 56]. Osteoblasts may also have a role in bone loss in gout. In vitro, MSU crystals inhibit osteoblast viability, differentiation and mineralisation, leading to a

reduced capacity for new bone formation at sites of MSU crystal deposition. These *in vitro* findings are supported by bone samples affected by tophus, as osteoblasts are noticeably absent at sites of erosion [57]. Factors produced within the tophus are also likely to tip the balance within bone to a pro-resorptive state. A recent study reported increased expression of receptor activator of nuclear factor- κ B ligand (RANKL) in tophus samples from patients with gout, whereas osteoprotegerin expression was largely absent [3]. IL-1 β and TNF- α expression within the tophus may also enhance bone resorption [2, 3].

Compared to bone erosion in gout, the mechanisms responsible for pathological bone formation in gout are unclear and require further research. As mentioned earlier, joints affected by tophus are more likely to have features of abnormal bone formation [46]. However, given that there is a lack of viable osteoblasts present at sites directly adjacent to tophus compared to sites away from tophus within the same joint [57], it is unlikely that the physical tophus itself directly drives this pathology, as the local cells required to form new bone are compromised. It is plausible that within the same joint, osteoblasts on bone surfaces that are not in direct contact with MSU crystals and tophus may be stimulated by factors secreted by the nearby tophus to increase bone production [58]. This could be part of a compensatory repair response to counteract the extensive bone resorption that occurs in tophaceous gout.

Similar to bone erosion in gout, loss of cartilage at sites of tophus is also likely to be promoted by interactions between the tophus and local cells. *In vitro*, MSU crystals have profound negative effects on chondrocyte and cartilage viability in a dose-dependent manner. Chondrocyte function is also impaired with downregulation of matrix protein gene expression of aggrecan and versican and reduced collagen protein secretion [59]. At the same time, chondrocytes exposed to MSU crystals also upregulate the expression of catabolic inflammatory mediators and degradative enzymes which may further degrade cartilage matrix [59, 60]. Histological examination of cartilage in tophaceous joints revealed only residual fragments of degenerate cartilage surrounded by tophaceous material; there was little or no intact hyaline cartilage remaining [59]. These findings indicate that chondrocytes in the presence of MSU crystals are unable to maintain normal cartilage matrix production, and cartilage in the presence of tophus is unable to repair itself and is eventually destroyed.

The consequences of tophaceous disease on tendon function in patients with gout are not known, but it is possible that tophi may disrupt the arrangement of collagen fibrils within the tendon which could impair tendon function [61]. The interactions between MSU crystals and tenocytes (tendon cells) have recently been assessed. *In vitro*, a rapid reduction in tenocyte viability is observed following culture with MSU crystals. Tenocyte function is also altered with reduced gene expression of tendon matrix proteins such as biglycan and

tenascin C. Interestingly, the expression of catabolic enzymes was also down-regulated in tenocytes cultured with MSU crystals [50]. This may be part of a protective mechanism to limit MSU crystal-induced degeneration of tendon matrix, although this is also likely to hinder tendon repair processes, as degradative enzymes are necessary for tendon repair and maintenance [62].

Therapeutics for Tophaceous Disease

The central strategy for effective treatment of gout is long-term urate-lowering therapy to a serum urate concentration low enough to achieve MSU crystal dissolution. The 2012 American College of Rheumatology (ACR) guidelines recommend that the presence of gouty tophi is a definite indication for urate-lowering therapy in an individual with gout [63••]. The ACR guidelines advise that for most patients with gout, the target serum urate concentration is <6 mg/dL (360 μ mol/L), but that for those with gouty tophi, a lower target serum urate of <5 mg/dL (300 μ mol/L) may be required to improve the signs and symptoms of disease. These recommendations are based on data from observational studies demonstrating that the velocity of tophus resolution is inversely related to serum urate concentration and that tophus resolution occurs only at concentrations <6 mg/dL [64, 38].

A recent systematic literature review has examined interventions for tophaceous gout [65]. Overall, the level of evidence was low with one report of two randomised controlled trials, two non-randomised studies and 69 case series and reports. The review concluded that treatment with urate-lowering therapy including allopurinol and/or benzbromarone, febuxostat or pegloticase can lead to reduction in tophi. The ACR guidelines recommend single-agent xanthine oxidase inhibitors (allopurinol or febuxostat) to maximum dose as first-line urate-lowering therapy, followed by the addition of a uricosuric agent [63••]. For those not achieving target serum urate concentration and continuing disease activity with this approach of oral medications, pegloticase is recommended for patients with chronic tophaceous gout.

Pegloticase is a PEG-conjugated mammalian recombinant uricase administered as an 8-mg intravenous infusion every 2 weeks. This agent converts urate to soluble allantoin, and in treatment responders, plasma urate falls to undetectable levels. In a report of two-phase three randomised controlled trials of patients with gout refractory to conventional therapy (69 % with tophi), treatment with fortnightly pegloticase for 6 months leads to significant improvements in serum urate concentrations, flare incidence, tender joint count, HAQ-DI and DSF-36 scores [66••]. In addition, a complete response in at least one tophus was observed over the 6-month period more frequently in the group receiving pegloticase every 2 weeks compared with the placebo group, 40 vs. 7 %,

respectively. Infusion-related reactions occurred in 26 % of participants receiving the bi-weekly infusion of pegloticase; subsequent analysis revealed that loss of serum urate response was a strong predictor of infusions reactions. For this reason, it is recommended that patients receiving pegloticase do not take additional urate-lowering therapy that might mask the loss of urate-lowering signal and that pegloticase not be administered to those who have not had a urate-lowering response (<6 mg/dL) with their previous infusion. The open-label extension studies of pegloticase have provided further information about the long-term impact of therapy on tophi, using a digital photography method of tophus assessment [67, 68]. After 1 year of pegloticase treatment, a complete response in at least one tophus (without any new/enlarging tophi) was observed in 70 % of the pegloticase-treated patients. A greater response was observed in pegloticase responders compared with non-responders.

In conjunction with intensive urate-lowering therapy, effective anti-inflammatory medications to both prevent and treat gout flares are required in patients with tophaceous gout. The 2012 ACR gout management guidelines recommend that low-dose colchicine or NSAIDs are most appropriate for first-line anti-inflammatory prophylaxis and that in the presence of gouty tophi, a longer duration of anti-inflammatory prophylaxis is indicated than for those without tophi, for at least 6 months after achieving the target serum urate concentration and longer if tophi are present on physical examination [69]. No specific recommendations are made for the management of an acute gout flare in patients with gouty tophi, with full-dose NSAIDs, colchicine or prednisone as first-line therapy. For polyarticular flares (which are more frequent in patients with tophaceous gout), combination therapy of colchicine with either NSAIDs or prednisone is also recommended.

Although medical management remains the mainstay of treatment for tophaceous gout, surgery is considered when there are complications of tophi including ulceration, infection, or severe joint damage and pain. In a retrospective analysis of 15 patients who underwent surgery for tophaceous gout at the MTP1 joint, tophus excision was compared with tophus excision and arthrodesis [70]. Pain scores, American Orthopaedic Foot and Ankle Society (AOFAS) score and patient satisfaction scores improved more in the excision/arthrodesis group, compared with the excision-only group. To date, there have been no randomised controlled trials of surgical interventions for the management of gouty tophi.

The observations that the osteoclast contributes to the development of bone erosion in tophaceous gout led to testing of the anti-osteoclast drug zoledronate for bone erosion [71]. In a 2-year randomised placebo-controlled trial, bone erosion scores did not change significantly over time following annual intravenous infusion of 5-mg zoledronate or placebo. Importantly, the participants in this study had mean serum urate

concentrations of 6.2 mg/dL (370 μ mol/L), i.e., at a level where existing MSU crystals within the joint were likely to be stable or only slowly dissolving. In contrast, in an exploratory study of eight patients with tophaceous gout treated with pegloticase, plain radiographic bone erosion scores significantly improved over a 1-year period [72]. All participants responded to pegloticase with serum urate <1 mg/dL (60 μ mol/L) during the treatment period. In contrast to the improvement in bone erosion scores, joint space narrowing scores did not alter following pegloticase treatment, suggesting that bone and cartilage may have different capacity to repair following dissolution of MSU crystals.

Conclusions

New research has provided important insights into the biology, impact and treatment of the gouty tophus. Although prolonged hyperuricaemia is a key risk factor for the development of tophi, it is unclear why some patients with gout develop tophi and others do not, even in the face of elevated serum urate concentrations for long periods. It is also unclear why tophi do not typically present with the cardinal features of inflammation (i.e., heat, erythema, swelling and pain), despite the presence of MSU crystals at the centre of these lesions. Optimal treatment strategies are also currently uncertain; is <5 mg/dL a low enough target? Should more rapid 'debulking' be employed routinely as induction therapy for patients presenting with gouty tophi? Despite these uncertainties, it is clear that the presence of gouty tophi represents persistent MSU crystal deposition and that tophaceous disease is associated with substantial musculoskeletal disability which impacts on many aspects of the patient's life. These observations argue for the earlier treatment of gout focusing on the strategy of serum urate lowering to achieve MSU crystal dissolution and to prevent the complications of longstanding hyperuricaemia including the development of tophaceous disease.

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Compliance with Ethics Guidelines

Conflict of Interest Nicola Dalbeth declares the receipt of consulting and speaker fees or grants from the following companies: Takeda, Teijin, Menorini, Ardea, AstraZeneca, Pfizer, Savient, Fonterra and Metabolex. Ashika Chhana declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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