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Review

Urate and osteoarthritis: Evidence for a reciprocal relationship

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ABSTRACT

Hyperuricemia is a common condition, and in a subset of patients leads to gout, the most common inflammatory arthritis. Osteoarthritis is the most common form of arthritis overall, and gout and osteoarthritis frequently coexist in the same patient. However, the relationship between the two remains poorly defined. More particularly, the impact of osteoarthritis on the development of gout, and the impact of gout on the development of osteoarthritis, remain to be determined. Additionally, whether hyperuricemia mediates osteoarthritis in the absence of gout is uncertain. Here, we review the evidence linking gout and osteoarthritis, with a special focus on the role of hyperuricemia in the presence or absence of gout. Since disease modifying agents are currently available for hyperuricemia and gout but not for osteoarthritis, a contributory role for urate in the pathogenesis of osteoarthritis could have important clinical implications.
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1. Introduction

Osteoarthritis (OA) is the leading cause of arthritis in the world, affecting 10–15% of adults, with a lifetime risk as high as 50% [1]. OA affects 30 million individuals in the US [2] and 302 million worldwide [3]. The prevalence of OA is rising and expected to affect 78 million US adults by 2040 [4]. OA is currently the 12th largest contributor to global disability [5]. In spite of the advances in understanding the roles of biomechanical stress and cellular responses in OA pathophysiology [6], approved pharmacologic therapy for OA remains limited to symptom relief, with no treatment available to prevent OA onset or progression.

Gout is the most common inflammatory arthritis, affecting 3.9% of US adults (8.3 million individuals) [7]. A necessary (but not sufficient) cause of gout is hyperuricemia, which is physiologically defined as a serum urate (sU) of > 6.8 mg/dL, the solubility point of monosodium urate (MSU) at pH 7.4. Hyperuricemia is much more common than gout, with prevalence in the US of 21.4% (~ 43 million individuals) [7]. The prevalence of asymptomatic hyperuricemia, defined as hyperuricemia in individuals without clinical features of gout is 17.5% (~ 35 million people). Asymptomatic hyperuricemia may be thought of as a biochemical/ metabolic condition, with the onset of gout representing a progression in some individuals to an inflammatory disease in response to MSU crystal deposition. Advanced imaging modalities have demonstrated that in about 25% of individuals, asymptomatic hyperuricemia is accompanied by tissue MSU crystal deposition [8,9]. The progression from asymptomatic hyperuricemia to gout often implies a state of increased MSU crystal deposition, including the formation of tophi, complex biologically-active structures reflecting chronic inflammatory granulomatous and fibrotic responses to MSU crystals [10].

While clinical experience suggests that gout and OA often occur in the same patient, whether there is a pathophysiologic relationship between OA and either gout or hyperuricemia is not clear. If hyperuricemia or gout promotes the development or progression of OA, this would have therapeutic implications given that, in contrast to OA, effective treatments for hyperuricemia and gout are available. We review here the relationship between OA and gout, and between OA and hyperuricemia.

2. Gout and OA: common clinical features and epidemiologic associations

Epidemiologically, gout and OA share a number of common risk factors, including older age and obesity. Prior joint injury is strong risk factor for OA, whereas acute joint injury has been associated with triggering gout flares. Gout and OA are also both associated

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with calcium pyrophosphate crystal deposition [11] in complex relationships that are beyond the scope of this review. In contrast, there are several discrepant risk factors, including gender (men more likely to develop gout, women more likely to develop OA) and renal insufficiency (a risk factor for gout but not for OA). While both diseases are influenced by genetic predispositions [12,13], the genetic associations for these diseases appear to differ, with OA genetics relating most commonly to cartilage biology and body mass index (BMI), and gout genetics relating largely to renal urate handling. Additionally, OA has been associated with IL-1β response genes [14], of potential relevance to gout since IL-1β is a central mediator of the gouty inflammatory response [15]. To date, variations in IL-1β response genes have not been associated with gout risk, though such associations have yet to be thoroughly evaluated among those with gout versus asymptomatic hyperuricemia.

OA and gout share a common proclivity for some particular joints, including the fingers (such as the distal interphalangeal joints), toes (particularly the first metatarsal phalangeal joints) and knees. In patients with nodal distal interphalangeal osteoarthritis, for example, gouty arthritis is not uncommon and has been associated with diuretic use and renal failure, presumably because of their impact on hyperuricemia [16]. Other joints differ however, with OA but not gout commonly affecting the hip, and gout but less commonly OA affecting the wrist (with the exception of patients who have experienced wrist trauma). Several studies have examined the articular localization of OA and gout. In 164 subjects with gout who were assessed for OA joint involvement by Roddy, et al., joints that had been the site of gout flares had a 7–8 fold higher odds of having OA compared with joints that had not experienced gout flares [17]. In another study, Dalbeth et al. reported that joints with dual energy CT (DECT)-evidence of MSU crystal deposition were 5–10 times more likely to have features of radiographic OA, including osteophytes, subchondral sclerosis, and joint space narrowing—features that are not typical of gout per se [18]. Similarly, a cadaveric study of the ankle, a joint not typically involved with OA apart from trauma, demonstrated that MSU deposits were co-localized with cartilage damage typical of OA [19] (Fig. 1). Thus, OA in individual joints appears to be associated with the presence of both clinically active gout and MSU crystal deposition. However, such observations do not prove causality. It is possible that both conditions occur due to shared risk factors such as obesity (BMI), age, and gender. Indeed, the relation of gout or serum urate to OA is often controversial due to concerns about adequacy of adjustment for these factors.

Clinically, gout is characterized by episodic flares of intense inflammatory arthritis. In contrast, painful flares in OA are less intense and more variable, including a potential participatory role for bone marrow lesions and synovitis [20]. Although OA has traditionally been considered “non-inflammatory”, synovitis and effusion are clearly evident on imaging, such as MRI and ultrasound, and there is often clinically evident joint swelling. Synovitis in knee OA is associated with inflammatory cytokines and with OA severity and progression [21,22], and its fluctuation over time parallels fluctuations in pain [23]. While synovitis is recognized in OA, why it occurs is controversial. One hypothesis is that synovium reacts to cartilage fragments and other debris by producing inflammatory mediators after becoming activated by triggering of the innate immune system [24]. Other evidence suggests that calcium crystals, whose formation often co-occurs in OA patients, may contribute to OA inflammatory responses [25,26]. Danger- and pathogen- associated molecular patterns (DAMPs, PAMPs) trigger the innate immune system and elicit an inflammatory response through interaction with particle recognition receptors such as toll-like and NOD-like receptors. MSU is one such DAMP, leading to inflammasome assembly and subsequent activation of inflammatory pathways [15]; whether these MSU effects are of relevance in the pathology of OA is not fully established. Further, whether the often-unpredictable fluctuations in OA pain may be related to urate crystals is an intriguing possibility.

Whether gout may predispose to OA, or OA may predispose to gout, has been only occasionally studied. In a UK case-control study involving 39,111 patients with incident gout, and an equal number of matched controls [27], medical records were reviewed for development of comorbidities for 10 years after the index date, and for the same period of time prior to the index date for preexisting comorbidities. Compared with controls, the risk of incident OA was higher in subjects with gout [hazard ratio: 1.45 (95% CI: 1.35–1.54)]. Subjects with gout were also more likely to have had a preceding diagnosis of OA (OR: 1.27) versus controls. BMI could not be fully accounted for, and therefore residual confounding cannot be excluded as an explanation for this observed association. Nonetheless, this report suggests that gout and OA may be risk factors for each other.

3. Hyperuricemia and OA: epidemiology and associations

The association between hyperuricemia per se and OA is best studied in patients with asymptomatic hyperuricemia, since it is nearly impossible to distinguish between urate and inflammatory effects in patients with established gout. Unfortunately, sU is not routinely assessed in many western countries, limiting the available clinical data with which to study this question.

We studied 75 older males from primary care clinics at a US Veterans hospital who were categorized as normouricemic, asymptomatic hyperuricemia, and gout (25 in each group) [28]. Our analyses included dedicated, standardized fixed flexion knee radiographs using a positioning frame. Using either ACR Clinical or Clinical/Radiographic classification criteria for knee OA, subjects with gout had more than a two-fold increase in prevalence of knee OA compared with controls (e.g., 68% vs. 28% for Clinical/Radiographic criteria). Those with asymptomatic hyperuricemia had a prevalence of knee OA that was intermediate between the normouricemic and gout groups (52% for Clinical/Radiographic criteria), suggesting a potential dose-response effect of hyperuricemia and the progression to gout on OA risk. The association with asymptomatic hyperuricemia was not seen in the subpopulation of obese patients, suggesting that obesity is a risk factor for OA that may overwhelm any hyperuricemia-specific effect. A similar finding was observed by Teng et al., who found that lean women with gout were more likely to undergo knee arthroplasty for severe OA than lean women without gout, but that this relationship did not hold for heavier women [29]. We further observed that asymptomatic hyperuricemia was associated with greater knee OA severity, and gout was associated with even more severe knee OA than the presence of asymptomatic hyperuricemia, again suggesting a dose effect [28]. In contrast to our observations however, Bevis et al. found no association between gout and knee OA, although an association between gout and foot OA was reported; here the impact of hyperuricemia was not studied [30].

To further explore the association between hyperuricemia and knee OA severity, we examined subjects’ knees and bilateral first MTP joints for the double contour sign (indicative of MSU crystal deposition on the cartilage surface) [31] and tophaceous deposits using musculoskeletal ultrasound. In these small studies, MSU crystal deposition was associated with higher prevalence of knee OA (60% vs. 27% OA prevalence, $P = 0.04$). Interestingly however, it was urate deposited in the first MTP rather than the knee that was associated with higher knee OA prevalence (for MSU crystal deposition in the MTP, 62.5% vs. 29% knee OA prevalence, $P = 0.03$; for MSU crystal deposition in the knee, 50% vs. 38.6% knee OA prevalence, $P = 0.6$) [28]. These data suggest that MSU

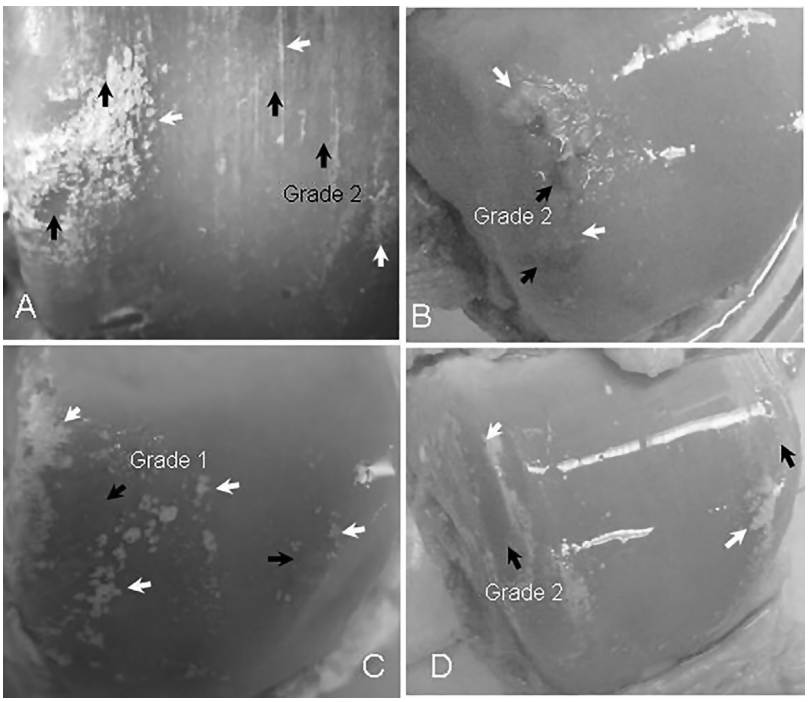

Fig. 1. Physical association between crystal deposition on cartilage and osteoarthritis, in cadaveric tali. Four examples in which crystal deposits (white arrows) are found to associate near areas of osteoarthritic cartilage denudation (black arrows). In more severe cases, the crystal deposition surrounds the cartilage damage. Grade 1 = early fibrillation, flaking, shallow pits or grooves and/or small blisters affecting the cartilage; Grade 2 = deep fibrillation and fissuring, flaking, pitting and/or blistering. Reprinted from Muehleman et al. [19]. With permission.

crystal deposition elsewhere may serve as a severity marker for hyperuricemia-related knee involvement. However, our study numbers were small, with an older age in our sample, and the effects of BMI were not fully accounted for.

Other studies have also supported a relationship between hyperuricemia and OA. For example, Ding et al. utilized a 4685-patient database in China (where sU is routinely assessed) and observed that the presence of osteophytes, characteristic of OA, was associated with hyperuricemia among females, but not males, even after adjustment for factors including BMI [32]. One limitation of this study was that the inclusion criteria did not distinguish between hyperuricemia with versus without gout, so asymptomatic hyperuricemia per se was not assessed.

4. Urate and OA: causality and pathogenesis

The epidemiologic relationship between hyperuricemia and OA raises the question of whether data support a biologic relation of the two entities. Four possibilities deserve consideration:

- the association between hyperuricemia and OA is due to shared risk factors (e.g., obesity), rather than any direct relationship;
- OA in a joint might promote urate crystallization locally, an effect that might be exacerbated in the setting of hyperuricemia and could lead to gout;
- MSU crystal deposition on/in cartilage may create local mechanical and/or inflammatory damage promoting OA development;
- urate may function intrinsically in the process of OA development and/or progression [33] (Fig. 2). These several possibilities are by no means mutually exclusive.

4.1. OA as a promoter of MSU deposition

A number of studies have addressed whether OA changes in the joint may predispose to MSU crystal formation [34]. Many of these emphasize the fact that crystallization requires a nucleation surface, and that OA cartilage may provide such a surface. Pascual et al. pointed out that MSU crystal deposition on cartilage occurs parallel to surface fibers, and suggest that the regular structure of collagen may provide the scaffold upon which urate may deposit [35]. Others have focused on the role of chondroitin sulfates (CSs), a set of molecules intrinsic to cartilage that may be exposed or released in the setting of OA cartilage degradation [36–39]. Among the multiple forms of CS, the greatest interest has focused on the relationship of CS4 to CS6. CS4 promotes urate precipitation whereas CS6 may retard it. Disruption of articular hyaline cartilage may lead to dispersal of CS6, found mainly at the surface, and exposure of CS4, found in deeper layers, resulting in an increased CS4/CS6 ratio and greater likelihood of urate precipitation. These processes would presumably be exacerbated in the presence of hyperuricemia, since synovial fluid is largely a hyperfiltrate of serum. It should be noted, however, that CSs may also attenuate macrophage activation [40], and so may reduce the inflammatory response to the crystals even as they promote urate crystallization. Finally, at least one study suggests that the synovial lining in OA may contribute to increased urate levels in the joint since OA synovium is more permeable to water than to urate. In this model, resorption of water from the joint fluid to the blood occurs more rapidly than urate resorption in the resting joint (for example, at night), such that a relative increase in urate concentration may be achieved. The authors suggest that this transient nocturnal increase in synovial fluid urate may be one reason that gout attacks typically happen at night [41].

4.2. Urate as a promoter of OA

Alternatively, urate could promote OA. Since cartilage damage of almost any sort may promote OA progression, it seems likely that mechanical damage from and/or inflammatory responses to MSU deposition and tophus formation could contribute to OA. Unfortunately, no study has formally assessed the impact of

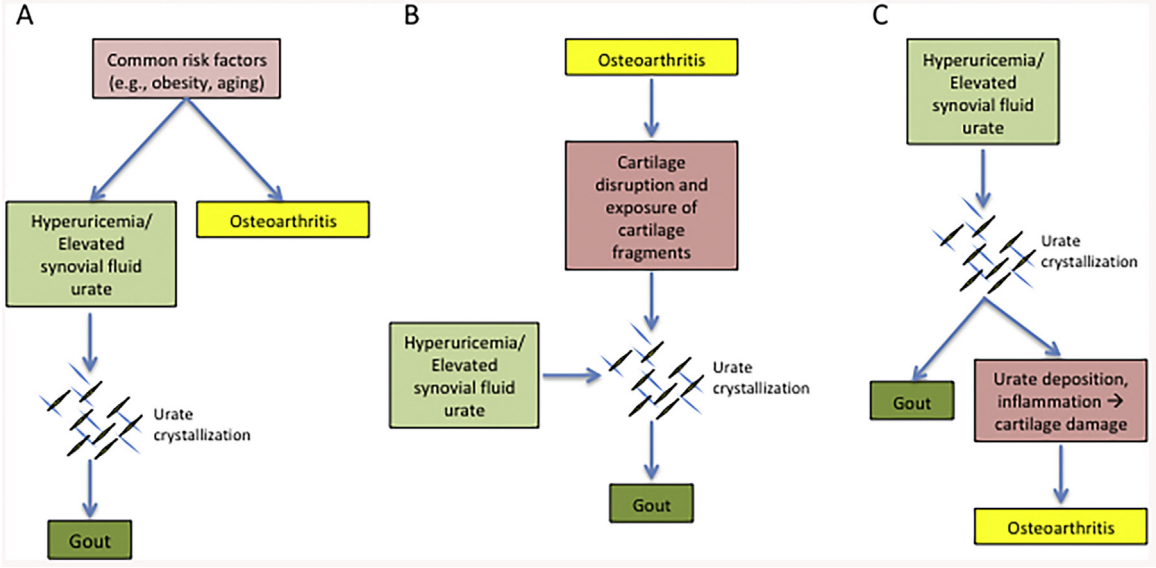

Fig. 2. Possible interactions between urate and osteoarthritis. A. Hyperuricemia and osteoarthritis are separately promoted by common risk factors such as obesity and aging. B. In the setting of elevated concentrations of urate in the joint, disruption of cartilage by osteoarthritis promotes urate crystallization and deposition that can lead to the acute inflammation of gout. C. Elevated levels of urate in the joint lead to urate crystallization and deposition on the cartilage, causing damage that leads to osteoarthritis. Adapted from Roddy and Doherty [33].

MSU/gout mechanical or inflammatory-mediated damage on OA progression.

Urate may also potentially play a biochemical role in OA pathophysiology. Once considered a condition of wear and tear, OA is now appreciated to be a mechanically-driven, but biochemically- and cellularly-propagated disease of the whole joint, in which expression of inflammatory mediators is a central and defining feature [42]. In response to mechanical and cellular stress, chondrocytes undergo phenotypic changes, elaborating mediators including IL-1β, TNF-α, PGE_2, nitric oxide and others [43,44]. The importance of IL-1β in particular may be underscored by the fact that polymorphisms of the IL-1β receptor antagonist gene are associated with OA severity [45]. Additionally, chondrocytes in OA secrete matrix metalloproteinases (MMPs) such as MMP-3 and 13, along with aggrecanases such as ADAMTS-4 and ADAMTS-5, effectively switching from an anabolic to catabolic phenotype [46]. Finally, OA chondrocytes demonstrate early aging and cell death [47]. These responses are associated with parallel responses in synovium, leading to the low-level synovitis that is a marker of OA severity [22], and to bony changes including subchondral sclerosis, osteophyte formation, and MRI-appreciated bone marrow lesions [48]. Evidence of the inflammatory nature of OA can also be gleaned from reports that elevated levels of IL-1Ra and PGE_2 in the plasma, and increased cytokine expression profiles in peripheral leukocytes, are associated with greater OA progression [21,49].

In vitro studies have demonstrated remarkably similar chondrocyte responses to MSU as those observed in OA. Liu, et al., reported that exposure of chondrocytes to urate resulted in up-regulation of IL-1β [50], consistent with the observation in other cell types that MSU can drive the NLRP3 inflammasome, the enzymatic activator of IL-1β and IL-18 [15]. MSU exposure also resulted in up-regulation of MMP-3, as well as inducible nitric oxide synthase (iNOS) up-regulation and nitric oxide production [50]. Chhana et al. documented similar findings and additionally reported that MSU caused chondrocytes to increase expression of ADAMTS-5 and decrease collagen production, and promoted chondrocyte death via a non-apoptotic process [51], in contrast to the expected process of apoptosis in OA [52]. This observation was subsequently confirmed and extended by Huang et al. who reported that urate-induced chondrocyte death proceeds through neither apoptosis nor necrosis, but through an autophagic mechanism [53]. The observation, first established by Shi, et al. that urate is generated by dying cells as a danger signal to alert the immune system [54], suggests that chondrocyte death in response to microcrystalline urate may in turn lead to the generation of additional urate, in a feed-forward amplification loop. Importantly, these responses only occurred at high concentrations of MSU, consistent with the likelihood of MSU microcrystal formation. However, not all urate exposure may be harmful to chondrocytes. Lai et al. reported that lower concentrations of urate—i.e., those below 6.8 mg/dL—may protect chondrocytes and prevent the development of an OA phenotype, including suppressing chondrocyte COX, MMP-13 and iNOS expression, and promoting collagen secretion [55]. Thus, urate may play an "either/or" role in cartilage, protecting against OA at low concentrations, but promoting OA at higher ones. Potentially consistent with this hypothesis, a number of studies have demonstrated the potential for urate to have either anti-oxidant vs. pro-oxidant properties depending on its environment [56].

Are these in vitro observations relevant to the human OA joint? Possibly. Denoble et al. examined the synovial fluid of 69 subjects with knee OA but without gout. They observed that synovial fluid concentrations of urate were correlated with synovial fluid levels of IL-1β and IL-18, consistent with the possibility that urate in the joint was activating the NLRP3 inflammasome, and that concentrations of these 3 analytes, along with TNF-α, correlated with measures of knee OA severity. They concluded that elevated synovial fluid urate levels may promote OA [57].

Since sU is a major determinant of synovial fluid urate concentration, we examined the possibility that sU may predict knee OA progression. Using data from 88 participants of a natural history knee OA cohort (for which a diagnosis of gout was an exclusion criterion) who had medial knee OA and serum available for baseline urate measurement [21,58], we observed that sU predicted progression of medial joint space narrowing. Higher sU levels were associated with more rapid joint space narrowing, with a threshold effect around a sU concentration of 6.8 mg/dL – consistent with the possibility of an effect of micro-crystalized but not soluble urate. Knee MRI was available in 25 of these subjects, in whom a linear relationship between sU and synovial volume was noted,

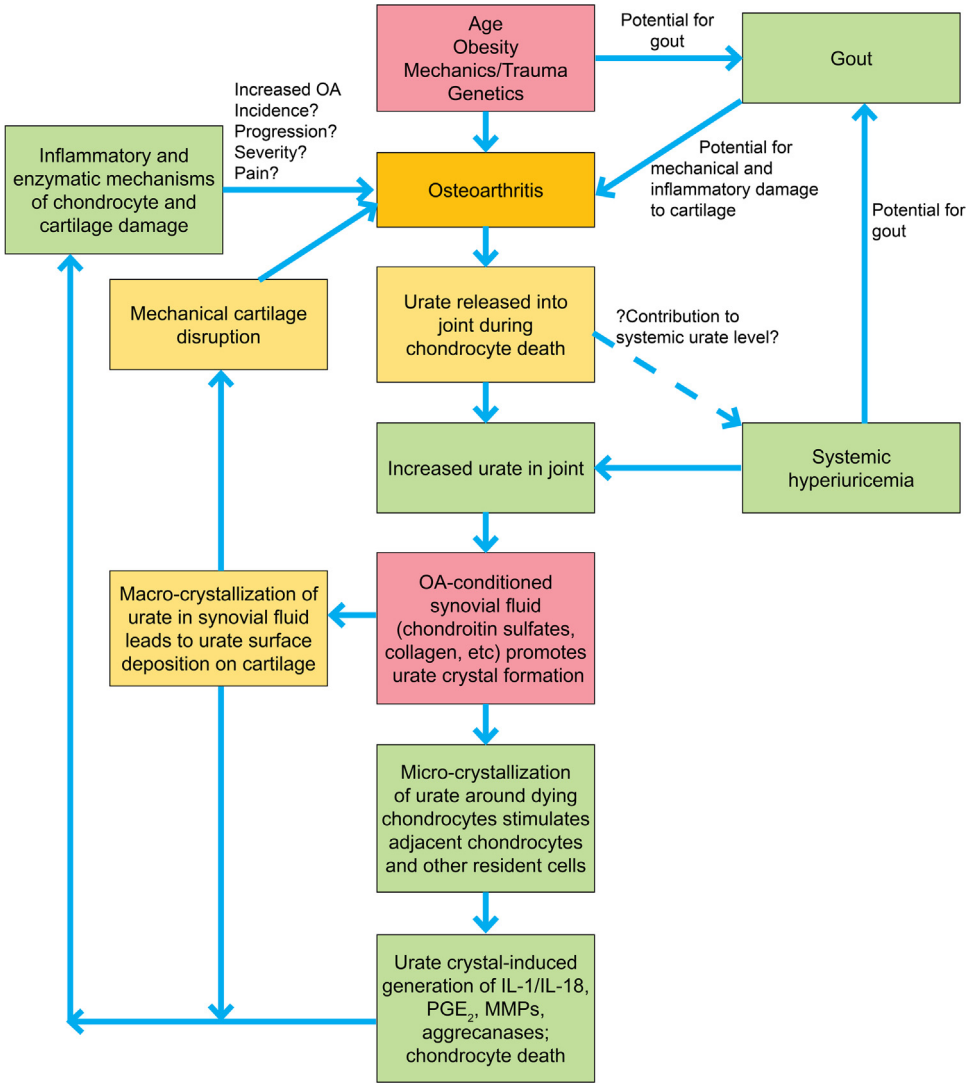

Fig. 3. Possible mechanisms of urate promotion of osteoarthritis. Processes that are more closely related to osteoarthritis are colored in yellow; processes that are more closely related to urate effects are colored in green; common or overlapping features are colored in pink. Please see text for details. Modified from Denoble et al. [57].

consistent with a possible impact of urate on synovitis in the setting of OA [59].

5. Modeling the interactions between urate and OA

While the above observations require confirmation, they suggest a model in which traditional risk factors (age, genetics, obesity, prior trauma or overuse, etc.) lead to the initial onset of cartilage damage, at least in the knee (Fig. 3). At that point, proteases released by the chondrocytes contribute to the degradation of cartilage, and inflammatory mediators are generated that promote inflammation, including of the synovium. At the same time, chondrocyte death leads to urate generation, which, if concentrations are high enough, may promote crystal deposition on the cartilage at a macroscopic level, potentially resulting in mechanical damage and/or inflammatory processes/responses to crystalized urate that makes the joint susceptible to additional OA progression. Crystal formation within the OA joint may be facilitated by the molecular products of OA itself (i.e., exposure of collagen and CSs from within the cartilage). Urate crystallization at the microscopic level, presumably around dying chondrocytes, could further activate neighboring chondrocytes to stimulate more protease and cytokine production, and promote additional chondrocyte death, by acting as a DAMP signal. The result would be a vicious cycle in which OA progression results in urate generation, and urate generation promotes further OA progression. In the setting of hyperuricemia, the OA synovial fluid will have higher background levels of urate, which may contribute directly to the local urate-mediated OA processes by increasing the likelihood of crystallization. In patients with frank gout, the risk of macroscopic MSU crystal deposition in the joint is increased (e.g., as articular MSU deposition and/or tophi), with the urate-/tophus-associated acute and chronic inflammation exacerbating the inflammatory processes already established in the OA joint, in addition to the potentially adverse mechanical effects of MSU crystal deposition. At the very least, such a model provides multiple testable hypotheses and suggests a number of possible points of intervention with currently available drugs. With the recognition of MSU crystal deposition on advanced imaging among people with asymptomatic hyperuricemia, longitudinal studies are needed to determine whether such deposition is a risk factor for development of OA, in addition to examining the longitudinal effects of hyperuricemia irrespective of asymptomatic MSU crystal deposition.

6. Conclusions

The old dogma—that OA was a disease of passive degeneration—inevitably led to a therapeutic nihilism that offered only surgical solutions. The increasing appreciation that OA is an

active, complex process involving all joint tissues has led to the view that biological intervention may someday prevent or slow the catabolic and inflammatory process. The overlap between OA and gout—and more particularly, OA and hyperuricemia—suggests that a co-occurrence that had been recognized clinically may not be merely coincidental. As our understanding of both OA and urate biology have increased in the last decade, it has become clearer that at least some mechanisms recognized in each are probably shared by both, suggesting the possibility of a reiterative relationship in which each condition may exacerbate the other. Given that OA structural disease is currently untreatable, whereas multiple drugs are available to manage hyperuricemia and gouty inflammation, the efficacy of urate-lowering therapies for OA becomes a testable hypothesis. In a single retrospective study, gout patients were more likely to undergo total hip or knee replacement than patients without gout, but gout patients receiving urate-lowering therapy were no less likely to undergo total joint replacement than those not receiving therapy. However, the study had several limitations, including the fact that the indications for joint replacement were not well defined, the degree of urate lowering achieved was not well-established, and the subjects in question had established gout (i.e., significant damage may already have accrued, in contrast to the case of asymptomatic hyperuricemia) [60]. Additional research is surely needed. Regardless of the outcomes of such investigations, the examination of OA and its interactions with hyperuricemia and gout have already yielded important knowledge about the biology and intersection of both conditions.

Disclosure of interest

The authors declare that they have no competing interest.

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