A Review of the Ophthalmic Manifestations of Gout and Uric Acid Crystal Deposition

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Abstract

Gout is a clinical disorder that is characterized by the deposition of monosodium urate crystals (MSU) in joints and tendons, usually in the presence of prolonged hyperuricaemia. Following an asymptomatic phase of hyperuricaemia, gout usually presents as acute monoarthritis followed by periods of remission and exacerbation. Conjunctival hyperaemia and subconjunctival haemorrhage exacerbated by purine intake are two of the more common manifestations that may go unrecognized. Other ocular and adnexal structures can be affected by urate crystal deposition and associated inflammation, with potentially vision-threatening consequences; however, ocular manifestations of gout are rare and may have been overeported in the older literature, but our understanding of the clinic-pathological features of ocular urate deposits remains limited.

Keywords: gout; ocular; ophthalmic; eyes; manifestations

Gout is a clinical condition that is characterized by the deposition of monosodium urate (MSU) crystals in joints and tendons, usually in the presence of prolonged hyperuricaemia.[1] The clinical manifestations of gout are divided into four phases: asymptomatic hyperuricemia, acute gout, intercritical gout and chronic tophaeceous gout.[2] In the acute phase, gout usually presents with a monoarticular arthritis followed by periods of remission and exacerbation known as intercritical gout. Analysis of synovial fluid for MSU crystals is paramount to achieving definitive diagnosis of gout but also in excluding septic arthritis which similarly presents as acute monoathritis. The transition to chronic gout is marked by the development of visible chalky white MSU deposits known as tophi in joints of hands or feet and not uncommonly on the helix of the ear, olecranon bursa or Achilles tendon.[1, 2] Rarer sites of urate crystal deposits include the breast, vocal cords, heart and colon.[3-6] Nephropathy and renal uric nephrolithiasis may be associated with progression of gout. Ocular manifestations of gout are rare, with most of our current knowledge derived from case reports spanning the past century. The aim of this review is to provide a current and consolidated summary of the ophthalmic manifestations of gout.

Epidemiology

Gout is the most common inflammatory joint disorder in men over 40 years of age.[7 8, 9]Studies have determined the prevalence of gout in USA and UK adult populations (age$\geqslant$ 20) to be similar, at 3.9% and 3.22% respectively. [8,9] The incidence in females increases following menopause, presumably due to falling levels of oestrogen, which has a uricosuric

effect.[10] The all-age prevalence of gout in the Australian population is 1.44% according to national surveys,[11] however, a higher prevalence is reported in the indigenous Australian population, with rates of 9.7% in men and 2.9% in women. [12] In New Zealand Pacific-islander and Maori populations, there is a threefold greater occurrence of gout compared to those of European descent,[13] suggesting the contribution of a combination of genetic predisposition and environmental risks to the development of gout in particular populations. Alcohol consumption, a diet high in seafood, fructose and red meat have traditionally been identified as risk factors for gout,[14-16] whilst conversely, coffee, dairy products, vitamin C and cherry are reported to be protective against the development of the condition.[17, 18] In addition, increased adioposity, insulin resistance, metabolic syndrome, renal impairment, cardiovascular disease and hypertension are recognized comorbidities that have been associated with an increased incidence of gout.[19]

Developed countries have a higher reported prevalence of gout compared to developing countries [9]Data regarding the epidemiology of gout in developing countries has been obtained from Community Oriented Program for the Control of Rheumatic Diseases (COPCORD) studies. In Central and South America, the prevalence of gout was 0.3% to 0.4% in Mexico, Cuba and Venezuela.[20-23] In Asian countries such as Bangladesh, China, India, Iran, Malaysia, Pakistan, Philippines, Thailand and Vietnam the prevalence of gout is less than 0.5%**,** [24-29] whilst**,** Indonesia has the highest known prevalence of gout in Asia,

Pathogenesis

Uric acid is the end product of purine metabolism (Figure 1). It has weak acid (pkA 5.8) that exists mainly in its ionized form as urate at physiological pH of 7.4 (consider flow chart for metabolism pathway. The absence of the hepatic enzyme uricase in humans and great primates has caused a tenfold increase in serum uric acid levels compared to mammals that possess the enzyme.[7] Hyperuricaemia arises from a disruption in balance between endogenous purine production, dietary purine intake and excretion rate. From population studies, a direct causal relationship has been identified between hyperuricaemia and the risk of gout.[30, 31] This relationship has been established by an 80% reduced risk for recurrent gout after treatment with urate lowering therapies.[32]

Urate production derives mainly from the liver and small intestine. Overproduction of urate, which accounts for 10% of hyperuricaemia, can result from recycled purine nucleotides in proliferative and inflammatory disorders such as psoriasis and haematological malignancies where there is increased cell turnover.[33] Increased fructose and alcohol consumption leading to accelerated degradation of adenosine triphosphate to adenosine monophosphate, a precursor of uric acid, is another cause of urate overproduction.[14, 16] , whilst inborn errors of metabolism that result in primary urate overproduction are estimated to account for less than 1% of gout-afflicted individuals.[7]

Two-thirds of produced urate is excreted renally while one-third is excreted through the gastrointestinal system. Impairment of renal excretion accounts for 90% of hyperuricaemia. Dysfunction of urate anion transporters, glucose transporter 9 and urate transporter 1, which mediate renal reabsorption of urate, have been implicated in the pathogenesis of gout.[34 35] In particular, URAT1 is a vital target for uricosuric drugs such as losartan.[36] Genetic variations

of these renal transporters may explain hereditary risks of developing gout and certain responses to anti-uricaemic medications.[33] Recently, dysfunction of ATP-binding cassette sub-family G member 2, an intestinal urate transporter has been identified as a significant cause of hyperuricaemia from extra-renal under-excretion.[37] Drugs such as low-dose salicylate, pyrazinamide and niacin are known to impair renal urate transporters although the evidence supporting increased risk of gout is unclear.[38]

In long-standing hyperurcaemia, supersaturation of uric acid results when the serum saturation threshold of 380 μmol/ is exceeded. This leads to the formation of monosodium urate (MSU) crystals that deposit predominantly in peripheral joints and surrounding connective tissue, which can manifest as visible tophi. MSU formation is dependent on local factors such as pH, urate concentration, temperature, cation concentration as well as presence of extracellular matrix proteins including chondroitin sulfate, collagen and proteoglycans.[33]

MSU crystals have been recognized to induce crystal-induced inflammation through several mechanisms(Figure 1). Recognition and subsequent phagocytosis of urate microcrystals by neutrophils, macrophages and mast cells stimulate the release of interleukin 1β, TNF (Tumour Necrosis Factor) α, CXC-Chemokine ligand, interleukin 6 and interleukin 8.[39] Phagocytosed urate crystals in macrophages and mast cells also activate an inflammatory cascade, eventuating in the release of interleukin 1β, which promotes neutrophilic influx into the joints.[39] Toll-like receptors (TLR) including TLR-2 and TLR-4 promote interleukin 1β and neutrophil recruitment,[40] whilst direct interaction between crystals and cell membranes leads to intracellular pro-inflammatory signaling in dendritic cells.[41] Chronic inflammation

associated with release of cytokines, chemokines, proteases and oxidants results in chronic synovitis, cartilage degradation and bone erosion.[33] Additionally, coating proteins at the crystal surface including complement components Cq1, Cr1, Cs1 promote inflammatory responses by stimulating neutrophil recruitment[42], whilst the spontaneous resolution of crystal-induced inflammation has been attributed to coating proteins such as apolipoprotein E.[43]

Ophthalmic manifestations

The ophthalmic manifestations of gout are rare but diverse. Urate crystal deposition has been observed in almost all ocular and adnexal locations, including the eyelid, conjunctiva, sclera, cornea, lens, iris, orbit, vitreous chamber, optic disk and retina. Additionally, ocular structures have relatively poor solvent ability in addition to lower temperatures and therefore are predisposed to tophi deposition. As a result of urate deposits, crystal-induced inflammation of the affected tissue is responsible for the clinical picture.

Periocular urate crystal deposition

Tophi deposition in the form of nontender subcutaneous masses in the upper eyelid[44], medial[45, 46] and lateral canthus[47] have been documented in several case reports. The appearance of these masses varied from a smooth, firm, white, chalky to yellow, and dome-shaped to a raised nodular skin-coloured lesion with central depression and superficial crusting resembling a basal cell carcinoma.[45-47] These affected individuals reported gradual enlargement of the mass without any other symptoms such as bleeding, inflammation, discomfort or any visual complaints. The occurrence of periocular tophi is extremely rare;

with these incidences confirmed by histological evidence of negatively birefringent urate crystals. Serum uric acid levels are a generally poor biomarker in these individuals and the authors suggest the ophthalmic findings may be an initial sign in undiagnosed individuals.[47,48]

Conjunctiva

Red eyes are a commonly reported feature of gout. In a prospective study by Ferry *et al*. on 69 patients with severe gout, bilateral conjunctival and episcleral vessel hyperaemia was the most common ocular feature with 62% of patients presenting with red eyes.[48] Lin *et al*.'s study of 380 individuals with gout from China, bulbar conjunctival vessels were markedly tortuous and dilated in a significantly greater percentage of patients with gout compared to the control group.[49] Moreover, multifocal, patchy subconjunctival haemorrhage was a universal finding in short and long-term gout sufferers. These haemorrhages failed to resolve within 3 months of follow up and were unresponsive to 2 weeks of topical tobramycin and dexamethasone. To our knowledge, the conjunctival vessel pathology in gout has never been reported and the pathophysiology underlying the presumed vessel fragility is unclear.

Subconjunctival transparent vesicles were another prominent feature in this Chinese population, with at least four times greater percentage in comparison to patients from the control group. The percentage of transparent vesicles doubled when the duration of gout was greater than 5 years.[49]

Chronic conjunctivitis also has been reported in two cases out of twenty-eight gout patients with ophthalmic presentation.[50]

Tophi deposition in the conjunctiva and sub-conjunctiva has also been documented.[51-54] In each of these cases, 1-2 mm chalky white crystal deposits were located temporally or nasally, often resembling pingueculae. All patients had an established diagnosis of gout. Under polarized light microscopy, the deposits were identified as negatively birefringent monosodium urate crystals.

Sclera and Episclera

Scleritis has been described in gout, manifesting as either anterior or posterior scleritis, and associated with tenonitis, characterized by severe pain, proptosis, chemosis and lid oedema.[51, 55] These cases of scleritis have been described in patients who had either coinciding features of gout, hyperuricemia or resolved scleritis after gout treatment with no other evidence to confirm the association between scleritis and gout.Scleral tophus deposition has been documented with a 3x4 mm chalky white uric acid deposit located nasally in the sclera.[49] The affected individual had significantly elevated serum uric acid in addition to concomitant tophi in both ears and feet.

Episcleral involvement has been reported to manifest in gout as either nodular episcleritis or more frequently as recurrent episcleritis (episcleritis periodica fugax).[51] Episcleritis periodica fugax presents with localized transient redness that lasts for a few days, disappearing in one portion of the eye only to appear in another quadrant in the same or opposite eye.[51, 56] Serpell reported 11 cases of episcleritis associated with gout over 24 years.[50]

Cornea

Tophus deposition has been reported in most layers of the cornea, including the corneal epithelium[49, 57], stroma[49, 58] and Bowman's layer[59]. The individuals in these case series presented with burning ocular pain, progressive redness and impaired vision. The deposits are fine, refractile, needle-like or punctate and most dense in the palpebral fissure. These crystals may resemble band keratopathy but differ in colour, being brownish rather than whitish grey. The deposits can be removed by scraping or superficial keratectomy

Hutchinson[60], described corneal ulcers associated with acute gout attacks that resolve with urate-lowering therapy. Marginal corneal ulcers associated with deposits resembling urate crystals have also been described;[56] but without histological confirmation.

Uvea

Iritis in gout has a sudden onset, a duration lasting up to 2-3 weeks, and rapid cessation.[51, 61] Between attacks, the eye appears mostly normal although occasionally there may be posterior synechiae formation. Treatment with colchicine and corticosteroids leads to rapid resolution of symptoms within three to four days.[61]

In the 1960s gout was estimated to cause 1-3.5 %[62] of all uveitis; however, more recently the prevalence of gout-related uveitis has decreased. Several cases have been reported of uveitis associated with hyperuricaemia that resolved with gout treatment.[62, 63] Yülek *et al* reported a case of gout-associated anterior uveitis with elevated intraocular pressure that required surgical control.[64] Disc swelling was also a feature in this individual.

Ferry *et al*. concluded that uveitis was an overestimated ocular complication of gout and not as common as previously thought. Similarly, Lin et al. in their 2013 population study of

Chinese residents, reported no cases of uveitis. These studies suggest that earlier cases of uveitis may have been falsely attributed to gout. Tophi deposition within the iris and anterior chamber has been reported.[65] On examination, multiple clear gelatinous deposits were found superiorly on the iris surface at the pupillary margin and inferiorly at the anterior chamber angle. Analysis of the anterior chamber aspirate and conjunctival biopsy revealed the presence of urate crystals.[65]

Lens

In an Australian population aged over 40, individuals with gout for greater than 10 years had a significantly higher risk of developing cortical cataract compared to age-matched controls.[66]

Orbit

A single case of an orbital mass consisting of urate crystals has been described. This individual presented with periocular pain and ptosis. Orbital imaging revealed a 2 cm superlateral mass extending to the frontal bone, and urate crystals were detected on histopathology.

Vitreous chamber

There are anecdotal reports of an association between gout and asteroid hyalosis [48, 67] However, epidemiological studies, including the Blue Mountains Eye Study[68] and the Yonsei Eye Study[69] found no significant association between gout and asteroid hyalosis.

Retina

In the 19th century, Hutchinson[60] reported that gout was associated with "retinitis haemorrhagica" (a central retinal vein occlusion). A recent case of simultaneous central retinal vein occlusion and branch retinal artery occlusion was described in a gout sufferer taking non-steroidal anti-inflammatory drugs for two weeks.[70] A causal relation remains unclear.

Intraocular pressure

Raised intraocular pressure was observed by Ferry *et al*.[48] in 10 out of 69 individuals with gout. Five individuals had open-angle glaucoma whilst the other five had ocular hypertension without glaucomatous nerve damage or visual field defect. The mechanism is unclear but is presumably caused either by anterior uveitis or a primary trabeculitis.

Dry eyes

Both the Beaver Dam Eye Study[71] and the Extension Blue Mountain Eye Study[72] found that a history of gout was independently and significantly associated with dry eyes. However, a follow-up study of the Beaver Dam Eye cohort measuring the 10-year incidence of dry eyes revealed no significant association with gout.[73]

Treatment

Treatment of ocular manifestions should be targeted towards the underlying gout. Recently published recommendations for effective gout treatments are separated into 4 specific management domains, covering acute and chronic presentations. An acute gouty

arthritis attack should be treated with pharmacologic therapy, initiated within 24 hours of onset and established pharmacologic urate lowering therapy should be continued, without interruption, during an attack of gout.[74] Nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids or oral colchicine are appropriate first line agents for treatment of acute gout, with selection influenced by co-morbidities, concurrent therapies and contraindications. Patient education on diet, lifestyle, treatment objectives and management of comorbidities and secondary causes of hyperuricaemia are recommended core therapeutic measures in chronic gout. Xanthine oxidase inhibitor (XOI) therapy with either allopurinol or febuxostat is recommended first line pharmacologic urate-lowering therapy in gout, with uricosuric agents (eg: probenecid) only used in first line if there is an absolute contraindication to a XOI and when creatinine clearance is $\geqslant$ 30mL/min.[75] Indications for urate lowering therapy include recurrent attacks (>1 attack per year), chronic arthropathy, tophaceous deposits, nephrolithiasis and radiographic changes of gout.[76] Starting dose of allopurinol should be no greater than 100mg/day, and less in patients with moderate to severe chronic renal disease, followed by a gradual upward titration of the maintenance dose which can often be greater than 300mg/day, dependent on tolerability, symptoms and achievement of target serum urate level. Target serum urate for prevention of acute gout attacks is at least 0.36mmol/L, although improvement of symptoms and signs, including tophi, may require a serum urate level of < 0.27mmmol/L. Patients need to be educated about the importance of compliance and educated about and monitored for the features of allopurinol hypersensitivity syndrome. Febuxostat can be substituted for allopurinol in the event of intolerance or adverse events. Starting dose is 40mg/day and may be increased to 80mg after 2 weeks if the target serum

urate level is not achieved. Probenicid is the recommended agent where uricosuric monotherapy is employed and is contraindicated in patients with a history of uric acid overproduction or urolithiasis and is ineffective in patients with a creatinine clearance ≤30mL/min. Combination therapy with an oral urate lowering therapy and a uricosuric agent is appropriate when symptoms persist and the serum urate target has not been met by appropriate dosing with an XOI.

Although the systemic management of gout is the primary strategy in the treatment of ophthalmic manifestations, local therapy targeted at the ocular inflammation may be utilized. The local treatment will need to be individualized and will depend on the severity and location of the associated inflammation. Hence, it is not practical to provide guidelines on the treatment of all the ophthalmic manifestations; however, comprehensive reviews on the current and future treatment of ocular inflammation are available.[77-79]

Conclusion

Gout is a systemic disorder characterized by the depositon of MSU in joints and connective tissue usually in the setting of prolonged hyperuricaemia. Conjunctival hyperaemia is a common occurrence in gout with unclear aetiology; however, other ocular manifestations are rare. Urate crystal deposition has been reported in most ocular structures, but vision threatening complications are unusual. Although there are various documented ophthalmic presentations attributed to gout in the literature, the evidence between many non-histologically proved presentations such as uveitis and their association with gout are tentative at best. At present, until further research into this area is able to more clearly

highlight their relation to gout, caution should be advised in the consideration of gout as a diagnosis in some of these presentations.

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Figure 1: Metabolic pathway of uric acid. Denovo synthesis begins with the combination of Ribose-5-Phosphate and a phosphate group from adenosine triphosphate (ATP) to produce Phosphoribosyl Pyrophosphate (PPRP) which is catalyzed by the Phosphoribosyl pyrophosphate synthetase (PPRPS) enzyme. In addition, purine bases derived from tissue nucleic acids are recycled through the salvage pathway. The enzyme hypoxanthine–guanine phosphoribosyl transferase (*HGPRT*) salvages hypoxanthine to inosine monophosphate (*IMP*) and guanine to guanosine monophosphate (*GMP*). Inborn errors such as HPGRT deficiency and overactivity of PPRPS are known to cause secondary gout. The conversion of adenine to adenosine monophosphate (AMP) by Adenine phosphoribosyl transferase (APRT) represents another salvage pathway. In the catabolic pathway, hypoxanthine is broken down to xanthine before being broken down to uric acid by xanthine oxidase.

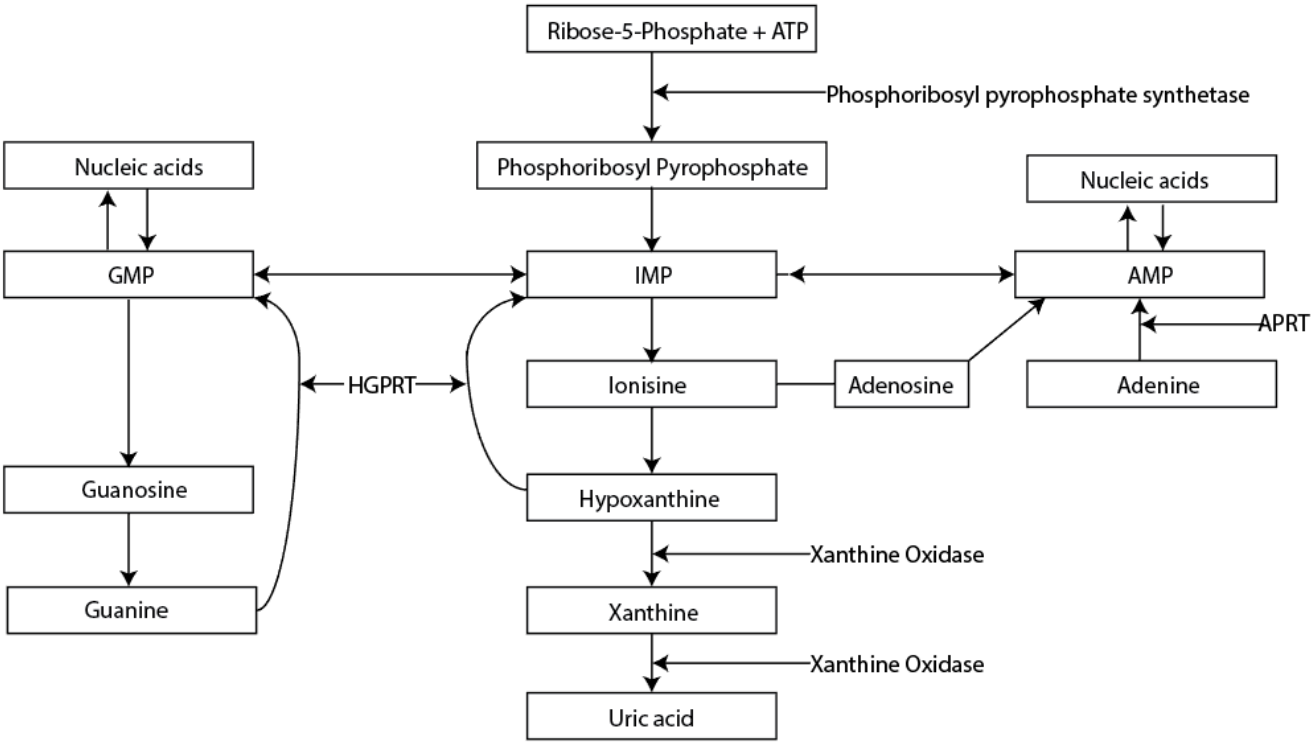
Ribose-5-Phosphate + ATP
Phosphoribosyl pyrophosphate synthetase
Phosphoribosyl Pyrophosphate
Nucleic acids
GMP
IMP
AMP
Nucleic acids
APRT
HGPRT
Ionisine
Adenosine
Adenine
Guanosine
Hypoxanthine
Xanthine Oxidase
Guanine
Xanthine
Xanthine Oxidase
Uric acid

Figure 2- Mechanism of crystal induced inflammation

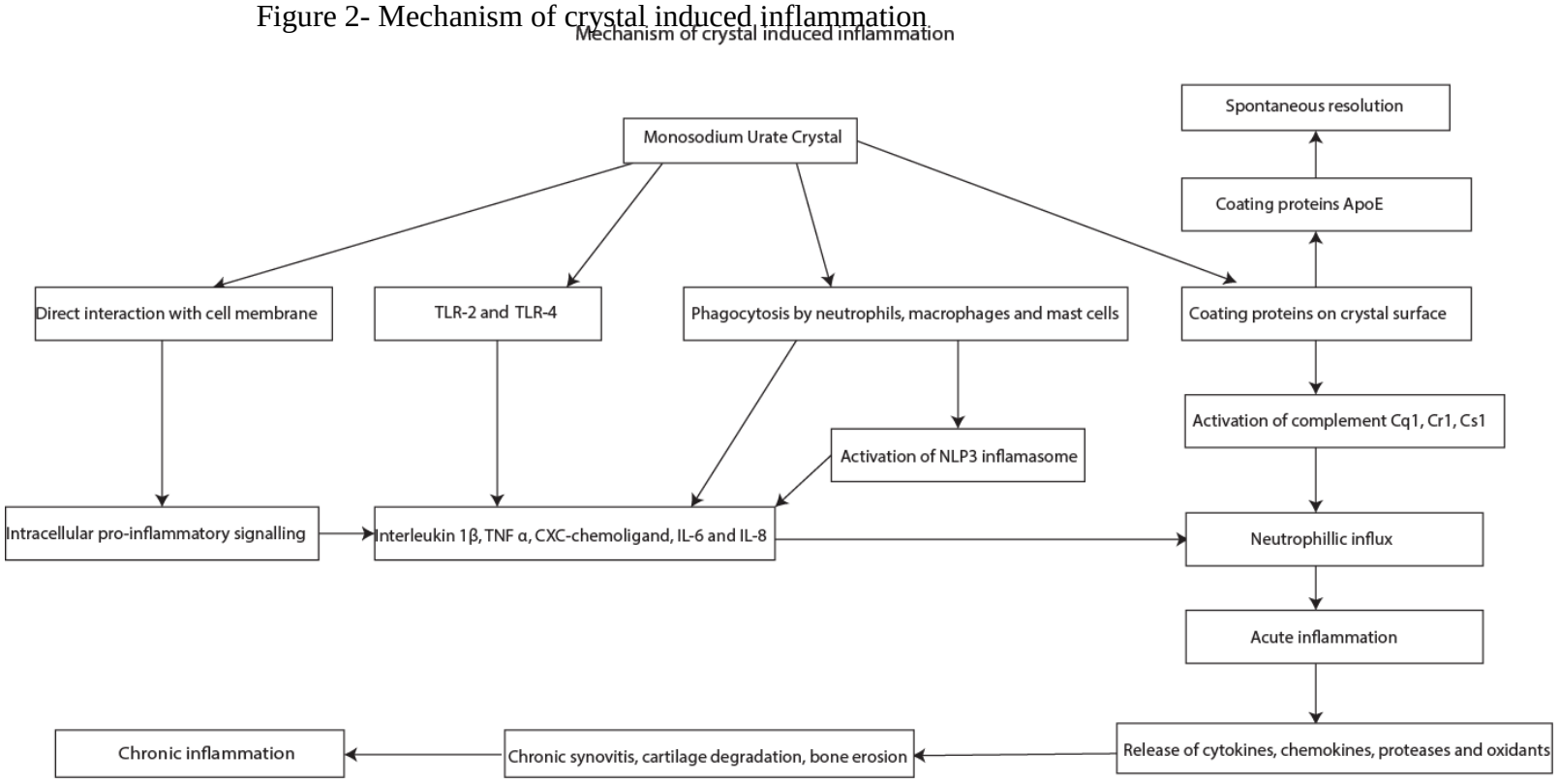

Table 1- Summary of ocular manifestations of gout

Location	**Manifestation**
Periocular region: Eyelid, lateral canthus, medial canthus	• Tophi deposition
Conjunctiva	• Bilateral conjunctival vessel hyperaemia, • Dilated and tortuous bulbar conjunctival vessels • Subconjunctival haemorrhage • Subconjunctival transparent vesicles • Chronic conjunctivitis
Sclera	• Tophi deposition • Scleritis ± tenonitis
Episclera	• Nodular episcleritis • Episcleritis periodica fugax • Episcleral vessel hyperaemia

Cornea	• Tophi deposition in corneal epithelium, stroma and Bowman's layer • Marginal corneal ulcers
Uvea	• Iritis • Uveitis • Tophi deposition within iris and anterior chamber
Lens	• Cortical cataract
Orbit	• Orbital mass of urate crystals- Periocular pain and ptosis
Vitreous body	• Asteroid hyalosis
Retina	• Central retinal vein occlusion and branch retinal artery occlusion
Optic Disc	• Optic disk oedema
Other	• Raised intraocular pressure • Dry eye syndrome