

Physiopathology of gout

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Introduction

Gout can be defined as the presence of monosodium urate crystals (MSUCs) in tissues. These MSUCs may induce acute inflammation when shed into the synovial fluid or cause aggregate-inducing chronic tissue inflammation.

The nucleation and formation of MSUCs is related to the presence of longstanding hyperuricemia, which is an essential factor in the development of gout. Other factors, such as level of hyperuricemia, time exposed to hyperuricemia, and genetic or acquired tissue predisposition for the nucleation of MSUCs, may explain why not all patients with hyperuricemia develop gout, or why some patients develop early or rapidly progressive symptoms associated with gout.

Genetic factors associated with hyperuricemia

The organic anion transporter family, located primarily in the proximal renal tubules, is responsible for most of the renal handling of uric acid. Multiple renal tubular transporters have been identified, but the most important ones seem to be uric acid transporter (URAT)1 [1] and URAT1v [2], with their lack of expression leading to renal hypouricemia types 1 and 2, respectively. Polymorphisms encoding hyperactive variants of these renal tubular transporters have been associated with increased risk of hyperuricemia and gout [3]. More recently, a new transporter, ABCG2 has emerged as a major contributor to impaired intestinal excretion of uric acid [4].

URAT1 is the product of the *SCL22A12* gene. It is expressed only in the kidney and is located in the epithelium of the proximal (but not the distal) renal tubules at the apical membrane (luminal side). URAT1-deficient mice and humans show complete loss of the capacity to reabsorb uric acid, with correspondingly extremely low serum urate (sUr) levels and increased risk of renal lithiasis [5]. The majority of the drugs known to exert a significant uricosuric effect share the ability to inhibit URAT1. In contrast, most diuretic medications that induce a rise in sUr also increase uric acid URAT1-mediated transport [5]. The most effective uricosuric drug tested in clinical practice is benzbromarone, a drug that exerts intense inhibition of URAT1 activity, although is not widely available for clinical use [6].

The facilitated glucose transporter Glut9 was also found to act as a voltage-driven urate transporter and is therefore also known as URATv1 (voltage-driven urate transporter 1) [2]. Located mainly in the kidney and in the liver, Glut9 is encoded by the *SCL2A9* gene and is present both in the apical and basolateral membranes of the proximal tubule epithelial cells [2]. It shows different substrate affinities compared with URAT1; it is not influenced by organic anions, and hexoses strongly inhibit uric acid transport via Glut9. There are two known variants or isoforms of Glut9 (long and short, or Glut9a and Glut 9b), each showing different functionality depending on the intracellular concentration of hexoses [7]. Functional cooperation between URAT1 and URATv1 may be needed for maintaining uric acid homeostasis at the renal level [8].

Recent genome-wide association studies of sUr have identified an adenosine triphosphate-binding cassette transporter from sub-family G, member 2 (ABCG2). It is a unidirectional transporter located in the renal tubule and intestines, and its lack of expression has been associated with decreased intestinal excretion of uric acid [9].

Because urate deposition is enhanced in joints with osteoarthritis or cartilage derangements, it has been suggested that genetic factors related to matrix glycoproteins may also influence the deposition of urate crystals acting as templates for nucleation [10].

Mechanisms of hyperuricemia

Hyperuricemia is uncommon in animals. Humans and upper apes show higher serum urate levels than other mammals due to the loss of expression of the gene encoding uricase [11], which cleaves uric acid to allantoin, a more water soluble purine end-product. Renal excretion makes up about two-thirds of uric acid excretion; intestinal excretion may comprise up to one-third of that in people with normal renal function (defined in Chapter 1), and may even increase in patients with impaired renal function.

Several mechanisms, either alone or in combination, may explain why sUr rises over the concentration expected for those with normal function: an increase in the production of uric acid and inefficient renal excretion (IRE) and intestinal excretion of uric acid (Figure 2.1).

Inefficient renal excretion of uric acid (‘renal underexcretion’)

Up to 90% of patients with gout show IRE of uric acid [12]. It is clinically and academically attractive to differentiate patients who have IRE of uric acid, as it may help to better understand the underlying mechanisms and facilitate differential diagnosis. As we can only ascertain the presence of IRE of uric acid, those patients showing efficient renal excretion will be classified as having increased production or decreased intestinal excretion (or ‘false overproduction,’ as shown later).

Different methods have been proposed to identify patients with gout who have IRE of uric acid: 24-hour urinary uric acid (24-Uur) excretion [13]; clearance of uric acid (CuA) [12]; the urine uric acid-to-creatinine ratio [14]; the uric acid excretion per glomerular filtration volume, or Simkin’s Index [15]; and fractional excretion of uric acid. Some investigators have even suggested a composite method to simplify this assessment [16]. The first two methods require 24-hour urine collection, whilst the latter three may be calculated using spot urine and blood samples.

Renal clearance gives an indication of the renal capacity to clear blood of any solute. Clearance of uric acid shows a good correlation with 24-Uur and fractional excretion in patients with normal renal function [17], but cumbersome 12- to 24-hour urine collections are needed to measure it.

Mechanisms and causes of longstanding hyperuricemia leading to gout

1. Primary

a. Increased production of uric acid (<10%)

- Idiopathic
- Phosphofructokinase deficiency
- Hypoxanthine-guanine-phosphoribosyl transferase deficiency
 - Partial (Seegmiller-Kelley Syndrome)
 - Complete (Lesch-Nyhan Syndrome)
- Phosphoribosyl-pyrophosphate-synthetase overactivity
- Glucogenosis (I, III, V and VII)

b. Inefficient excretion (>90%)

- Idiopathic (transporter overactivity)
- Familial juvenile nephropathy with hyperuricemia (uromoduline mutation)

2. Acquired

a. Increased production

- Exogenous (diet related)*
- Ethanol
- Purines and animal proteins
- Increased cellular turnover*
- Extensive psoriasis
- Chronic myeloid/lymphoid proliferative diseases
- Chronic corpustrular hemolythic anemia

b. Inefficient excretion

- Medications*
- Diuretics (high-dose thiazides)
- Transplant agents (cyclosporine A, tacrolimus)
- Salicylic acid, phenylbutazone (low dose)
- Antibiotics (pyrazinamide, ethambutol)
- Anti-HIV agents (didanosine, ritonavir)
- Diet related*
- Sweetened (fructose-rich) food and drink
- Hypercaloric diet (insulin resistance)

c. Renal diseases

- Arterial hypertension
- Chronic renal disease

Figure 2.1 Mechanisms and causes of longstanding hyperuricemia leading to gout.

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Fractional excretion is an inexpensive method that uses spot blood and urine samples, and has been found to correlate with clearance in patients with normal renal function [18]. Only fractional excretion and clearance remain unchanged in patients treated with xanthine oxidase inhibitors (XOI) [12] and may be used to estimate IRE of uric acid in patients with ongoing XOI use. A limitation to the use of fractional excretion is that it is not useful in patients with decreased glomerular filtration rate [17].

Increase in uric acid production ('overproduction')

An increase in uric acid production may be due to several different mechanisms. It is generally assumed that this increase comprises 5–10% of all causes of hyperuricemia [12].

One mechanism of overproduction is through genetic alterations that lead to defects in the enzymes responsible for uric acid metabolism, leading to an increase in endogenous uric acid production. These kinds of anomalies, such as in Lesch-Nyhan Syndrome or glycogen storage disease type I (von Gierke's disease) and V (McArdle disease), among others, are rare enzyme deficiencies. A second mechanism is the increase in cellular turnover that may be seen in several different corpuscular anemia or lymphoid or myeloid proliferative conditions [19]. Another is excessive exogenous supply of purines due to a diet rich in high purine-containing food [20]. There is no way to ascertain a mechanism of overproduction, although genetic testing can be carried out when there is a definite suspicion of a genetic cause.

Impaired intestinal excretion

Recently, Ichida et al. showed that decreased activity of the ABCG2 transporter was associated with decreased intestinal excretion of uric acid and renal overload, or 'false overproduction' [4]. Therefore, patients with normal renal function and efficient renal excretion may have either increased production of uric acid or decreased intestinal excretion of uric acid.

Until genetic tests for these transporters become inexpensive and widespread for clinical practice, evaluation of renal excretion of uric acid (fractional excretion for patients with normal renal function and

clearance of uric acid for patients with chronic kidney disease) will remain the only clinical clue to the mechanism causing hyperuricemia.

Mechanisms of inflammation and joint damage in gout

The deposition of MSUCs in the joints seems to first appear in the surface of the hyaline cartilage. There is a shedding of crystals to the synovial fluid that may sensitize resident monocytes into active pro-inflammatory macrophages that would react when primed with new fresh crystals (Figure 2.2) [21]. There appears to be a threshold to induce acute, symptomatic inflammation, as chronic subclinical inflammation has been found in synovial fluid of asymptomatic joints showing persistence of MSUCs [22], and there is a presence of power-doppler signal in patients showing MSUC deposition by ultrasonography [23] (see Chapter 3 for imaging).

The NALP3 inflammasome has been recently considered to be one of the major routes of crystal-induced inflammation. The inflammasome is a protein complex component of innate immunity; activation of NALP3 induces activation of caspase 1 that cleaves pro-interleukin 1 into interleukin-1 β (IL-1 β). Interleukin-1 β interacts with its receptor (which is dependent on toll-like receptors), activating a myeloid-differentiation protein (MyD88) that induces nuclear factor-kappa B and thus the release of several pro-inflammatory cytokines, metalloproteases, and radical

Arthroscopic view of a knee joint with gout

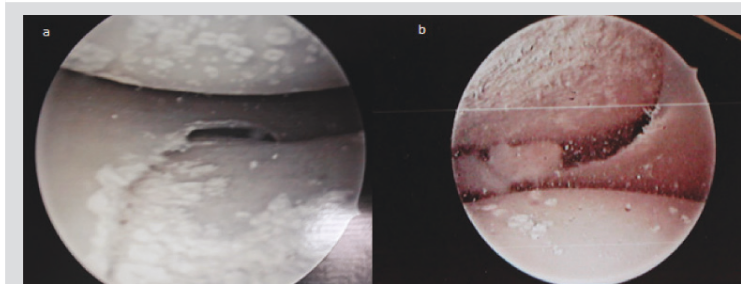


Figure 2.2 Arthroscopic view of a knee joint with gout. Deposition of MSUCs is initiated in the surface of hyaline cartilage (a). Crystals may shed into the synovial fluid (b) due to mechanical stress or changes in physiochemical conditions. Published with kind permission of © F. Perez-Ruiz 2014. All Rights Reserved.

oxygen species (ROS) [24]. The final result is an intense recruitment of neutrophil leukocytes that can be observed in synovial fluid heavily infiltrating the synovial membrane (Figure 2.3) [25].

An increase of MSUC deposition in the cartilage surface and consistent shedding into the synovial fluid will lead to their deposition in the synovial membrane, resulting in chronic granulomatous ‘foreign-body’

Synovial fluid and synovial membrane findings during the acute episodes of inflammation

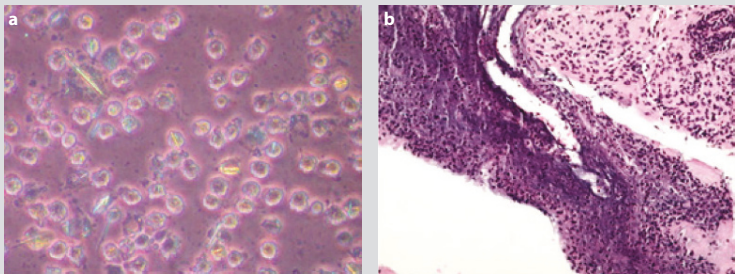


Figure 2.3 Synovial fluid and synovial membrane findings during the acute episodes of inflammation. The load of crystals into the synovial space may trigger phagocytosis by phagocytes (a: synovial fluid sample; polarized, contrast-phase microscopy, 400x), activate different cascades of inflammatory responses, and induce further recruitment through acute neutrophilic infiltration of the synovial membrane (b: synovial membrane biopsy, hematoxylin-eosine). Published with kind permission of © F. Perez-Ruiz 2014. All Rights Reserved.

Chronic urate-induced granulomatous synovitis

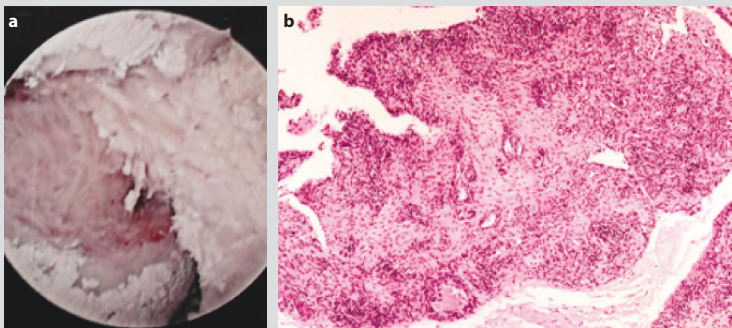


Figure 2.4 Chronic urate-induced granulomatous synovitis. Persistence of MSUCs in untreated or undertreated gout induces chronic synovial membrane inflammation (a: arthroscopic view), with chronic granulomatous ‘foreign-body’-like inflammatory reaction (b: synovial membrane biopsy showing epithelial palisades and multinucleated cells, hematoxylin-eosine). Published with kind permission of © F. Perez-Ruiz 2014. All Rights Reserved.

inflammation (Figure 2.4). The granulomatous reaction to the deposition of MSUCs has been studied in tophaceous deposition, showing that a large number of cells express IL-1 β [26]. Therefore, IL-1 seems to be a mediator of both acute and chronic inflammation, which makes IL-1 blockade a promising therapeutic target in gout [27] (see Chapter 5).

The development of MSUC deposition associated with chronic inflammation within the joint, or intra-articular tophi that may not be perceived in clinical examination [28], seems to be the mechanism for the development of bone erosions and, later, permanent structural damage of the joint [29].

Chronic inflammation in gout and its association with cardiovascular outcomes

Currently, there is a great interest in the impact of hyperuricemia on cardiovascular (CV) outcomes; nevertheless, in most countries urate lowering medications are not approved for the treatment of asymptomatic hyperuricemia.

The impact of hyperuricemia on CV events has been shown to be mild-to-moderate in recent systematic reviews and meta-analyses [30,31]. A meta-analysis that included 26 studies of over 400,000 adults only found a significant association between hyperuricemia and coronary heart disease (CHD) incidence or mortality in women, not in men [30]. A modest association was found between hyperuricemia and stroke when over 200,000 patients from 16 eligible studies were pooled for meta-analysis [31]. In none of the studies included in either meta-analysis was the presence of gout considered as a variable, so it is not known for certain how many patients actually had gout [32].

When ‘presence or absence of gout’ is available as a variable for analysis, a certain independent and significant association between a gout diagnosis and CV outcomes has been noted, even when other associated confounding variables such as CHD, heart failure, and myocardial dysfunction have been included [33–35]. Put simply, the difference between hyperuricemia and gout is that gout is a condition in which deposition of MSUCs in tissue has occurred, eliciting acute, chronic, and even sub-clinical inflammation.

Asymptomatic longstanding hyperuricemia is associated with urate deposition and subclinical inflammation previous to clinical gout development. In patients with longstanding asymptomatic hyperuricemia, urate deposits were observed in 34% and power-doppler signal was present in 66% [23].

Subclinical inflammation is present in asymptomatic joints of patients with gout [22]. Ultrasonographic evidence has supported this, as synovial hypertrophy and moderate-to-marked power-doppler signal was observed in 68% and 28%, retrospectively, of 78 first MTP joints of 39 patients, despite the fact that 22 of them were on NSAIDs [36].

Extensive MSUC deposition is associated with chronic histopathologic inflammation, elevated C-reactive protein, and CV outcomes. As previously mentioned, tophi represent a complex and organized chronic inflammatory tissue response to MSUCs [26]. It is agreed that the highest burden of MSUC deposition is the chronic inflammatory response, so the question that remains is to ascertain whether severity of gout, as a hallmark of the burden of deposition, is associated with CV outcomes.

In one cross-sectional study that included hyperuricemia as a confounding variable, an increased number of affected joints was independently associated with Q-wave myocardial infarction in electrocardiogram registries in all patients (men aged >50 years) and the presence of tophi was associated with the same outcome in patients aged <50 years [37]. More recently, a study based on the prospective long-term follow-up of a cohort of patients has shown that tophaceous gout is also associated with increased risk of mortality, in most cases due to CV origin [38].

Treatment of gout with colchicine decreases MSUC-induced inflammation and CV events. Colchicine therapy has been shown to reduce leukocyte counts in synovial fluids of asymptomatic joints containing MSUCs [39]. In a recent cross-sectional, retrospective study of over 12,000 patients, those who had ever been treated with colchicine had a lower rate of myocardial infarction that persisted whether or not allopurinol intake was considered as a confounding variable [40]. Patients treated with colchicine also exhibited trends toward reduced all-cause mortality and lower C-reactive protein levels [40].

Key points

- Prolonged hyperuricemia is the fundamental contributing factor to MSUC formation.
- Both genetic and environmental factors contribute to the development of hyperuricemia, and therefore of gout. Local tissue factors may also be a factor in MSUC nucleation and growth.
- Persistence of MSUCs may trigger both acute inflammatory responses and chronic inflammation responsible for the later destruction of osteoarticular structures.
- Recent data show an association between chronic urate deposition and CV events that may occur through the persistence of chronic subclinical inflammation.
- A greater burden of deposition may be linked to poorer CV outcomes.

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