New insights into the epidemiology of gout

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Gout is a true crystal deposition disease caused by formation of monosodium urate crystals in joints and other tissues. It is a common inflammatory arthritis that has increased in prevalence in recent decades. Gout normally results from the interaction of genetic, constitutional and environmental risk factors. It is more common in men and strongly age related. A major determinant is the degree of elevation of uric acid levels above the saturation point for urate crystal formation, principally caused by inefficient renal urate excretion. Local joint tissue factors may influence the topography and extent of crystal deposition. Recent studies have provided information on dietary risk factors for gout: higher intakes of red meat, fructose and beer are independently associated with increased risk, whereas higher intakes of coffee, low-fat dairy products and vitamin C are associated with lower risk. Several renal urate transporters have been identified including URAT1 and SLC2A9 (GLUT9) and polymorphisms in these genes are associated with an increased risk of hyperuricaemia and gout. Many drugs influence serum uric acid levels through an effect on renal urate transport. Comorbidities, including the metabolic syndrome and impaired renal function are common in gout patients. The usual initial presentation of gout is with rapidly developing acute inflammatory monoarthritis, typically affecting the first MTP joint. If left untreated it may progress with recurrent acute attacks and eventual development of chronic symptoms and joint damage. New knowledge of the modifiable risk factors for gout can be integrated into the management strategy to optimize long-term patient outcomes.

Key words: Gout, Epidemiology, Prevalence, Incidence, Hyperuricaemia, Risk factors, Urate transport.

Introduction

Gout is an increasingly common condition in both primary care and specialist practice. It is the most common inflammatory joint disease in men and the most common inflammatory arthritis in older women. After a long period with little clinical or research attention to gout, there has been a recent resurgence of interest in this condition. This article will review the most recent information on the epidemiology of gout and hyperuricaemia and set the scene for the following two papers that address aspects of gout management.

Incidence and prevalence of gout and hyperuricaemia

The epidemiology of gout is difficult to quantify precisely due to variations in methodology between studies, including differences in case definition and in the means of estimating incidence and prevalence. However, there is no doubt that it is a very common condition and studies from several countries, particularly in the USA, report an increase in prevalence in recent decades [1].

Data from a large managed care database in the USA indicate that the unadjusted prevalence of gout increased from 2.9/1000 people in 1990 to 5.2/1000 people in 1999 [2]. The prevalence particularly increased in those aged >65 years, especially men aged >75 years in whom the prevalence doubled (Fig. 1). Interestingly, this increased prevalence in older men and women was largely attributed to primary, not secondary gout. Other US data published in 1998 gave an overall prevalence of self-reported gout of 8.4/1000 people (across all ages, races and both sexes) and an estimated total number of cases in the USA of 1.56 million men and 550,000 women [3]. A more recent study suggested that the number of self-reported cases of gout in the USA had increased from 2.1 million to 3.0 million over a 10-year period, making it more prevalent than RA (estimated 1.3 million affected adults) [4, 5]. Other US studies support an increase in prevalence both of gout and hyperuricaemia in the past few decades, as well as a possible worsening of gout severity at presentation with more patients having tophi and upper limb involvement at the time of diagnosis [2, 6].

On the other hand, data from the UK suggest that the prevalence of gout increased during the 1970s and 1980s [7], but then stabilized during the 1990s [8]. In a study utilizing the large UK General Practice Research Database (GPRD), the unadjusted prevalence of gout in 1999 was 1.4%, with the highest rate of 7.3% being observed in men aged 75–84 years (Fig. 2) [8]. A more recent study in Germany and the UK showed the same 1.4% prevalence of gout in both countries over the period 2000–05 [9]. The yearly incidence rates for the UK derived from the GPRD for 1990–99 showed modest increases in the early 1990s in older men and women but a return towards 1990 values by the end of the decade. The GPRD data also showed that only approximately one-third of the patients diagnosed with gout received urate-lowering drug therapy.

All studies have consistently shown that gout predominantly affects older men. Presentation is unusual before the age of 45 years, but in men older than this both the incidence and prevalence of gout increase with age. Most studies show an overall male:female ratio of approximately 3–4:1. In a recent study in a northern European population, ~80% of the gout cases were men [9]. In the USA, the ratio was reported to be 4:1 below the age of 65 years and 3:1 above this age, reflecting the rarity of gout in younger women but the age-associated increase in gout in post-menopausal women [2].

Where an increased incidence and prevalence of gout has been reported, it is generally attributed to trends in lifestyles leading to increases in gout risk factors, such as obesity, metabolic syndrome, hypertension and alcohol consumption [1]. Annemans et al. [9] identified a high incidence of comorbidities, such as obesity, diabetes and hypertension in gout patients in the UK and Germany. Age is also a risk factor so the ageing of the population is likely to increase the incidence of gout. In hospital practice, complex cases of gout, particularly secondary gout, are becoming more common, with the increasing prevalence of advanced chronic kidney disease and the use of diuretics and nephrotoxic drugs being possible contributing factors [1].

Hyperuricaemia is very common and, depending on the definition, a prevalence of up to 15–20% has been reported in population-based studies [8]. Hyperuricaemia is recognized as one of the main risk factors for gout [10–12] although only a minority of individuals with elevated serum uric acid (SUA)
levels ever develop gout, emphasizing the importance of factors other than the ionic product in determining crystal formation. Studies have shown that the higher the sUA, the greater the risk of gout. In a cohort of more than 200 asymptomatic men, the annual incidence was 0.5% in those with baseline sUA <7 mg/dl and the cumulative incidence was 22% after 5 years. In comparison, the annual incidence was 0.5% in those with initial sUA 7–8.9 mg/dl and 0.1% in those with sUA <7 mg/dl [13].

Urate production/excretion

In common with other higher primates, many birds and some reptiles, man lost the ability to produce the enzyme uricase due to a series of parallel mutations in the Miocene period. Uricase converts uric acid (relatively insoluble) to allantoin (highly soluble), and hence due to this evolutionary event, uric acid levels are higher in man than in many other animals. However, interestingly, man is the only mammal to spontaneously develop gout.

Endogenous production of uric acid from degradation of purines usually contributes about two-thirds of the body urate pool, the remainder being dietary in origin. Of the uric acid produced daily, the majority (~70%) is excreted via the kidney and the remainder is eliminated into the biliary tract and subsequently converted by colonic bacterial uricase to allantoin. In the vast majority of people with gout, hyperuricaemia results from reduced efficiency of renal urate clearance [14, 15].

Risk factors

Multiple risk factors may interact and lead to development of gout.

Genetics

Monogenic disorders that result in overproduction of uric acid via enzyme defects in purine metabolism are extremely rare. Nevertheless, common primary gout in men often shows strong familial predisposition, although the genetic basis remains unknown. Twin studies have shown high heritability for both uric acid renal clearance (60%) and uric acid: creatinine ratio (87%) and several susceptibility loci for this have been reported [1].

Recent interest has particularly focused on genes regulating urate transport. The SLC22A12 gene codes for human urate transporter 1 (URAT1), a member of the organic anion transporter family that, together with other recently identified transporters, is important in controlling reabsorption of uric acid from the renal tubules. A polymorphism of this gene has been associated with ‘under-excretion’ of uric acid and hyperuricaemia in German Caucasians [16] and a URAT1 mutation has been shown to be protective for development of gout in a Japanese cohort [17]. The glucose and fructose transporter SLC2A9 (GLUT9) has recently been shown to act as a high-capacity urate transporter in proximal renal tubules [18]. Polymorphisms in this gene have been reported to influence sUA levels [19, 20] and a significant association with self-reported gout has been described [21]. The association between polymorphisms in SLC22A9 and both sUA level and risk of gout was confirmed in a recent study of three large cohorts [22]. The same investigators also identified two further gene associations, ABCG2 and SLC17A3, allowing development of a genetic score to predict risk of gout.

The epidemiology of gout in New Zealand exemplifies gene–environmental interaction and the importance of lifestyle factors in development of gout [1]. The Maori have marked genetic predisposition to hyperuricaemia and gout. However, prior to the 18th century it appears that Maoris never experienced this dramatic joint disease. Following the imposed extreme changes in diet and lifestyle that followed European settlement, gout appeared in the Maori and showed an increase in prevalence in the 20th century to possibly the highest in the world (one in eight Maori men recorded in 1992 [23]) (Fig. 3). In three identically conducted surveys, there was a doubling of prevalence recorded from 1958 to 1992 [1, 23], as well as an increase in proportion of patients with tophi, a younger age of onset of gout and an increase in familial cases [23]. The latter was not due to new mutations that cause gout, but to the fact that genetically predisposed people are more prone to develop gout if exposed to additional risk factors, such as altered diet, increasing weight and an increase in alcohol (see below).

Gender, age and OA

Men have higher urate levels than women and an increased prevalence of gout at all ages, though less pronounced in older age. Oestrogen has a uricosuric effect, making gout very rare in younger women. However, after the menopause, urate levels rise and gout becomes increasingly prevalent. Ageing is an important risk factor in both men and women, possibly due to multiple factors including: an increase in sUA levels (mainly due to reduced renal function); increased use of diuretics and other drugs that
raise sUA; age-related changes in connective tissues, which may encourage crystal formation; and an increased prevalence of OA. A recent clinical study showed a significant association between the joints involved in acute attacks of gout and the presence of OA suggesting that the tissue changes that occur in OA may encourage local deposition of MSU crystals [24]. Conversely, there appears to be a negative association between RA and both gout [25, 26] and calcium pyrophosphate crystal deposition [27] suggesting that the RA joint environment is not conducive to crystal formation.

Diet

Historically, gout has long been linked with a rich lifestyle involving excesses of meat and alcohol, but it is only recently that population studies have been undertaken to determine the risk associated with individual dietary components.

Data from the large Health Professionals Follow-up Study (HPFS) have shown that the relative risk of gout is higher in people who eat a high red meat diet: the relative risk of a first attack of gout associated with an additional daily portion of meat was 1.21 (95% CI 1.04, 1.41). Higher consumption of seafood was associated with a lesser, but still significant, increase in risk. Diets high in purine-rich vegetables did not increase the risk, while diets high in low-fat dairy products were associated with reduced risk (relative risk with additional daily serving 0.79; 95% CI 0.71, 0.87) [28].

Further data from the HPFS showed an association between the consumption of soft drinks sweetened with sugar (but not diet drinks) and new incident gout cases. The adjusted risk of gout in the highest quintile of fructose intake was twice that in the lowest quintile ($P < 0.001$ for trend) [29]. Fructose is known to raise the serum urate level and several mechanisms probably contribute to this, possibly including the SLC2A9 (GLUT9) transporter discussed earlier [19]. It is unclear whether this is a particular effect of fructose derived from corn, which is the main sweetener used in the USA, or whether it extends to sucrose (a disaccharide of fructose and glucose), which is the main sweetener used elsewhere in the world [30]. However, the USA does seem to have a particularly strong combination of lifestyle risk factors for primary gout and has led the current pandemic of obesity and metabolic syndrome, perhaps largely explaining the higher increases in incidence and prevalence seen in the USA.

Vitamin C has a modest uricosuric effect and in the HPFS, there was an inverse relationship between vitamin C intake and sUA [31]. In a randomized placebo-controlled trial, vitamin C supplementation (500 mg/day) for 2 months resulted in a significant reduction in $\text{sUA}$ of 0.5 mg/dl (~20% of the starting values) [32]. There are anecdotal reports that consumption of cherries has a beneficial effect on gout and this is supported by a recent study showing a decrease in urate levels after consumption of cherries but not other fruits [33]. The mechanism for this, and whether it relates to differential vitamin C content, is not clear. Consumption of coffee, but not green tea (both contain high levels of caffeine), has been reported to be associated with lower sUA levels in Japanese men [34], and recent data from the HPFS have confirmed an inverse relationship between coffee consumption and the risk of incident gout [35]. Again, this effect appeared independent of caffeine intake, suggesting that other, as yet unidentified components of coffee are causal in this respect.

In a 7-year prospective study of almost 29,000 healthy male runners, the risk of self-reported incident gout was lower in men who were more physically active, with a low BMI, with diets including more fruit and less meat and alcohol [36], supporting the benefit of lifestyle changes in reducing the risk of gout.

Alcohol

Some alcoholic drinks are rich in purines, notably beer which contains guanosine. Alcohol is thought to increase the risk of gout because the metabolism of ethanol to acetyl CoA leads to adenine nucleotide degradation, resulting in increased formation of adenosine monophosphate, a precursor of uric acid. Alcohol also raises the lactic acid level in blood, which inhibits uric acid excretion. In the HPFS, overall the higher the daily alcohol intake, the higher the risk of gout [37]. However, differences in risk were observed with different alcoholic drinks. Beer had the greatest effect, probably because of its high purine content, then spirits, whereas wine had no increased risk [38].

Drugs

Many drugs which either increase sUA levels (e.g. diuretics and pyrazinamide) or reduce sUA levels (e.g. uricosurics such as benz-bromarone, sulphinpyrazone and vitamin C) effect these changes via interaction with urate transporters such as URAT1 [38] and GLUT9 [19].

The use of both loop and thiazide diuretics is widely regarded as one of the most common modifiable risk factors for secondary gout, especially in the elderly and in women [11, 39, 40]. One recent case-control study suggested, controversially, that the association between diuretic use and gout did not persist after adjustment for cardiovascular risk factors [41]. However, this study was probably underpowered, so it has been recommended to still follow advice in recent guidelines [11, 42] to discontinue diuretics in gout patients if feasible [43].

Aspirin has a bimodal effect on urate levels: low doses inhibit uric acid excretion and increase urate levels, while high doses (>3000 mg/day) are uricosuric. In elderly patients, aspirin at a dose of 75 mg/day associates with a small but significant increase in sUA ($P = 0.009$) [44]. While this is unlikely to be important in individuals, the effect could be significant at a population level, because of the widespread use of low-dose aspirin.

Cyclosporin is an independent risk factor for new onset gout in solid organ transplant patients, and together with other comorbid risk factors such as obesity and hypertension, it probably contributes to the high incidence of hyperuricaemia and gout in this population [45, 46]. In transplant patients, gout and tophi may progress rapidly and be particularly severe, polarticular, and challenging to manage. A possible mechanism for cyclosporin-induced hyperuricaemia has been identified recently, with the observation that cyclosporin interacts with the hOAT10 transporter that mediates urate/glutathione exchange in the kidney [47].
Renal disease and gout

Gout frequently associates with kidney disease, each being a risk factor for the other [48]. Primary kidney disease can lead to hyperuricaemia and it has been suggested that the increasing prevalence of end-stage renal disease may be one cause of recent increases in gout [1].

Kidney damage secondary to gout is associated with urate crystals and microtophi in the interstitium and/or uric acid crystals within tubules. Evidence from animal studies suggests that hyperuricaemia may accelerate chronic kidney disease, and several studies have demonstrated a significant and independent association between sUA levels and the progression of chronic kidney disease [49, 50].

A history of gout is an independent risk factor for urolithiasis in men [51]. The increased risk is not just for uric acid stones, but also for more common calcium phosphate stones. High urinary levels of uric acid increase the risk of stone formation and in gout patients, the higher the excretion of uric acid, the greater the risk of stone formation [52]. However, the most important risk factor for uric acid stone formation is persistently acidic urine, favouring the precipitation of urate [53]. In patients with uric acid stones, a high urinary urate:creatinine ratio indicates overproduction of uric acid, which should prompt a search for an abnormality of purine metabolism.

Metabolic syndrome

Hyperuricaemia is an integral part of the metabolic syndrome, together with hypertension, obesity, dyslipidaemia and insulin resistance. One Korean study showed a prevalence of metabolic syndrome (defined by the National Cholesterol Education Program – Adult Treatment Panel criteria [54]) of 44% in gout patients compared with 5% in historical controls [55]. In a US population, the metabolic syndrome (defined by the same criteria) was present in 63% of those with gout compared with 25% of those without gout [56]. In men at increased risk for cardiovascular events, a diagnosis of gout associates with a significantly increased risk of the future development of Type II diabetes, even after adjustment for sUA levels [57]. In the HPFS, obesity, weight gain and hypertension have all been shown to be independent risk factors for the development of gout [58].

Pathophysiology of gout

Gout is a true crystal deposition disease in which (i) the clinical symptoms are caused by the formation of monosodium urate (MSU) crystals in the joints and soft tissues and (ii) elimination of the crystals ‘cures’ the disease. For crystals to form and gout to occur, the ionic product of sodium and uric acid must be at or above the saturation level at which MSU crystals can form (Fig. 4). Uric acid is a weak acid with a pK_a of 5.75 and, at physiological pH of 7.40 it exists mainly in the ionized form as urate. MSU has limited solubility under physiological conditions and the saturation level in plasma at a pH of 7.40 is 6.8 mg/dl (408 µmol/l); when the plasma concentration exceeds this, crystals may form in the joints and tissues [14, 15]. Blood levels of uric acid are a surrogate for tissue levels within joints, but numerous observations support the use of a serum level of ≈ 6.0 mg/dl (≈ 360 µmol/l) as the therapeutic target for urate-lowering therapy [42]. Although a high ionic product is a pre-requisite for crystal formation, the balance of tissue inhibitors or promoters of crystal formation help determine whether any crystals form. We know little about such tissue factors. However, in OA it appears that the balance is in favour of crystal formation, not just of MSU [24] but also calcium pyrophosphate and basic calcium phosphate crystals.

MSU crystals preferentially form within cartilage and fibrous tissues, where they are relatively protected from contact with inflammatory mediators and may reside for years without causing problems. However, if ‘shed’ from these sites of origin into the joint space or bursa, they are highly phlogistic particles that are quickly phagocytosed by monocytes and macrophages, activating the NALP3 inflammasome, triggering the release of IL-1 and other cytokines and a subsequent infiltration of neutrophils [59]. This acute inflammatory response causes the symptoms of an acute flare and is typically self-limiting. Persistent accumulation of large numbers of MSU crystals may also cause joint damage through mechanical effects on cartilage and bone (‘pressure erosion’), and possibly low-grade inflammation, although these more chronic crystal-tissue interactions remain ill-understood.

Presentation of acute gout and differential diagnosis

Gout usually presents as acute inflammatory monoarthritis, typically affecting the great toe MTP joint (‘podagra’). Other joints that are frequently affected include the mid-foot, ankle, knee, wrists and finger joints. Attacks frequently start in the early morning, waking the patient from sleep. The rapid development of severe pain (‘worst ever’) and tenderness that reach their maximum within just 6–24 h of onset and then resolve spontaneously, usually within several days to 2 weeks, is almost pathognomonic of crystal synovitis. The vast majority of first attacks only affect a single joint but oligo-articular and polyarticular gout can occur especially in elderly patients [60]. It is suggested that the targeting of distal joints, particularly of the lower limbs, results from the lower temperature of the extremities which reduces the solubility of MSU [14]. Characteristic targeting of the first MTP joint may reflect the high prevalence of OA at this site which additionally encourages MSU deposition.

Acute gout attacks can be triggered by direct trauma to a joint, dehydration or acidosis, and rapid weight loss. A common trigger is intercurrent illness or surgery that causes an acute-phase response; this associates with lowering of sUA (through increased urinary excretion [61]) which may cause partial dissolution of MSU crystals and thus encourage crystal shedding. The same explanation is given for the increased incidence of attacks following initiation, or increase in dose, of urate-lowering therapy. A dose-response relationship between recent alcohol intake in the previous 48 h and risk of an acute gout attack [62], and an association between recent diuretic use and recurrent gout attacks [63] have both been reported recently.

Definitive diagnosis of gout is by identification of MSU crystals by polarized light microscopy in the aspirate from a joint or tophus (Fig. 5) [12]. Typically, MSU crystals are large (10–20 µm long) needle-shaped crystals, showing strong light
The differential diagnosis also includes other causes of acute monoarthritis, such as septic arthritis (usually more subacute and progressive) and occasionally PsA or ReA and palindromic rheumatism. Septic arthritis can be excluded by culture and Gram stain of the synovial aspirate. However, it should not be forgotten that gout and septic arthritis can co-exist [68].

**Natural history of the disease**

Gout is considered a progressive disease that, without effective long-term treatment, may eventually progress to severe tophaceous gout, with joint damage and significant functional impairment. It is commonly divided into the following phases: initial asymptomatic hyperuricaemia; recurrent acute gout attacks interspersed with asymptomatic intercritical periods; and chronic symptomatic tophaceous gout. As already mentioned, not all subjects with hyperuricaemia develop gout and a long period of asymptomatic hyperuricaemia may precede the first acute attack. Furthermore, these are not discrete phases but a continuum. MSU crystals and low-grade inflammation frequently persist in the affected joint in the intercritical period after the symptoms have resolved [69, 70]. Moreover, a recent ultrasound study has shown that deposition of MSU crystals in the tissues can occur before the first gout attack [71]. In this study, microtophi were detected in the joints and tissues of one-third of the subjects with asymptomatic hyperuricaemia, often with evidence of inflammation (increased vascularity). Once a patient has experienced a first attack, further attacks are likely to occur.

From a diagnostic perspective it is important to note that the sUA level typically decreases during an acute attack due to triggering of the acute-phase response and accompanying increased urinary urate excretion [61]. Hence, the most appropriate time to measure the sUA for future monitoring purposes is when the acute attack has completely resolved.

**Quality of life**

Several studies have shown that severe treatment-refractory gout is associated with lower functional status and quality of life compared with the normal population [72, 73]. The presence of acute attacks and tophi were associated with significantly lower scores in the Physical Component Score of the SF-36 [73]. However, since gout is mainly managed in primary care, it is important to assess the impact on quality of life in less severely affected patients in the community. In one community study comparing 137 patients with a history of gout with 2848 control patients identified in the same practices, the gout patients had significantly impaired overall quality of life, physical quality of life and satisfaction with health. Much of the adverse effect on quality of life was attributed to associated medical and musculoskeletal comorbidities but after adjustment for comorbidities, even in this population with relatively mild disease and few tophi, the effect of gout on the physical domain of quality of life remained significant [74].

**Conclusions and clinical implications**

In conclusion, gout is a very common form of arthritis that may be increasing in prevalence as a result of changes in diet, lifestyle and environmental factors. Although not life-threatening, it has a significant impact on quality of life. Symptoms are caused by the deposition of MSU crystals in joints and other tissues, when the ionic product for sodium urate exceeds the saturation point and when the balance of tissue inhibitors and promoters of crystal formation is in favour of crystallization. Hence, the objective of long-term therapy in those people with gout is to reduce the sUA level sufficiently that crystals can no longer form and that existing crystals are dissolved. Hyperuricaemia is the central risk factor for gout and is a key component of the metabolic pathway and a negative sign of birefringence. The presence of MSU crystals during an acute attack has the highest diagnostic value for gout (Fig. 6) [12]. However, a typical presentation of acute gout such as podagra, in a hyperuricaemic patient, is a reasonable basis for diagnosis in clinical practice [12]. MSU crystals can also be identified in a high proportion of fluids aspirated from uninflamed joints (first MTPs and knees) during an intercritical period, even if those joints have not previously suffered an acute attack [64].

The differential diagnosis of gout includes other crystal arthropathies, principally acute pseudogout caused by calcium pyrophosphate dihydrate (CPPD) crystals. Under polarized light microscopy CPPD crystals appear as small rhomboid crystals with low light intensity and a negative sign of birefringence. MSU and CPPD crystals may co-exist [65], especially in SFs aspirated from OA knees of older patients. Since age is a risk factor for both crystal arthropathies, MSU preferentially deposits in OA joints [24] and OA predisposes to CPPD deposition [66, 67]. Other intrinsic crystals, such as oxalate, are a very rare cause of synovitis.
syndrome. Hyperuricaemia is also an independent risk factor for cardiovascular disease, although at present there is no evidence to support urate-lowering therapy for asymptomatic hyperuricaemia.

As more is learnt about the pathophysiology, risk factors and comorbidities of gout, these findings can be integrated into a management strategy that encompasses patient education and lifestyle changes as well as pharmacological management to achieve optimal long-term patient-centred outcomes.

### Rheumatology key messages

- Gout is common, increasing in prevalence and hyperuricaemia is the central risk factor.
- Other risk factors include genetic predisposition, age, male gender, obesity, diet/lifestyle and OA.
- Management should include patient education/information access, lifestyle advice and urate-lowering therapy when appropriate.

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