

Update on factors predisposing to gout

Recent genetic, epidemiological and clinical studies have confirmed multiple factors predisposing to gout. Polymorphisms have been identified in genes encoding renal urate transporters and inflammatory cytokines. Epidemiological studies have established alcohol, dietary factors, hypertension, obesity, insulin resistance, diuretic therapy and chronic renal disease as independent risk factors predisposing to gout. In addition to the well-recognized influence of dietary purines, causative roles have been suggested for fructose and sugar-sweetened soft drinks, and protective roles for dairy products, coffee and vitamin C. Gout makes an independent contribution to the development of diabetes and cardiovascular disease. Osteoarthritis appears to predispose to local crystal deposition, but is not a risk factor for the development of gout *per se*.

KEYWORDS: alcohol, diet, diuretics, epidemiology, genetics, gout, hypertension, hyperuricemia, metabolic syndrome, osteoarthritis

Gout is one of the most common inflammatory arthritides. Recent studies undertaken in primary care databases in the UK and Germany have estimated the prevalence of gout to be approximately 1.4% [1,2]. Prevalence and incidence in the UK between 1990 and 1999 were both stable. However, data from the USA and New Zealand suggest that the prevalence and incidence of gout is rising [3–6]. Gout associates with impaired quality of life, which persists even after adjustment for the considerable comorbidity associated with gout [7,8].

The primary risk factor for the development of gout is elevation of serum urate (SUA) levels or hyperuricemia. Uric acid is derived either from dietary purines or the breakdown of endogenous purine nucleotides. In humans, uric acid is the end product of purine metabolism and is excreted either via the kidney or the gut (FIGURE 1). In lower mammals, uric acid is further metabolized to allantoin via the action of the enzyme urate oxidase (uricase). The ability to produce uricase was lost in primates following a series of missense mutations in the Eocene period. Hyperuricemia arises either as a result of overproduction or underexcretion of uric acid. As SUA levels rise and exceed the physiological saturation threshold of urate, monosodium urate (MSU) crystals form and are deposited in and around joints, manifesting clinically as acute gouty arthritis, tophaceous deposition of MSU crystals in joints and other tissues, chronic arthropathy and renal stone formation. Several risk factors predisposing

to hyperuricemia and gout are recognized (BOX 1), and are now discussed in turn (epidemiological data is summarized in TABLE 1).

Genetic factors

Patients with gout very commonly have family members affected by the disease. Several rare but well-described inborn errors of metabolism are known to affect purine metabolic pathways and cause gout. For example, Lesch–Nyhan syndrome is caused by complete deficiency of hypoxanthine-guanine-phosphoribosyl transferase (HGPT) manifesting as choreoathetosis, learning difficulties, self-mutilation, spasticity and hyperuricemia. However, such monogenic enzymatic defects are rare. A recent study of 983 patients with gout identified only one case of partial HGPT deficiency [9]. Point mutations have been identified in exons 2 and 3 of the *HGPT* gene. In the vast majority of cases of familial gout, inheritance is thought to be polygenic.

Genome-wide linkage scans in Taiwanese Aboriginal populations have revealed potential susceptibility loci in the 1q21 region of chromosome 1 [10] and the 4q25 region of chromosome 4 [11]. A further Taiwanese study compared the frequency of an estrogen receptor gene thymine–adenine dinucleotide repeat polymorphism located at chromosome 6q25.1 between 196 patients with gout and 102 unrelated healthy controls [12]. Patients with gout had fewer thymine–adenine repeats than control subjects (men: mean 14.9 vs 17.2; women: mean

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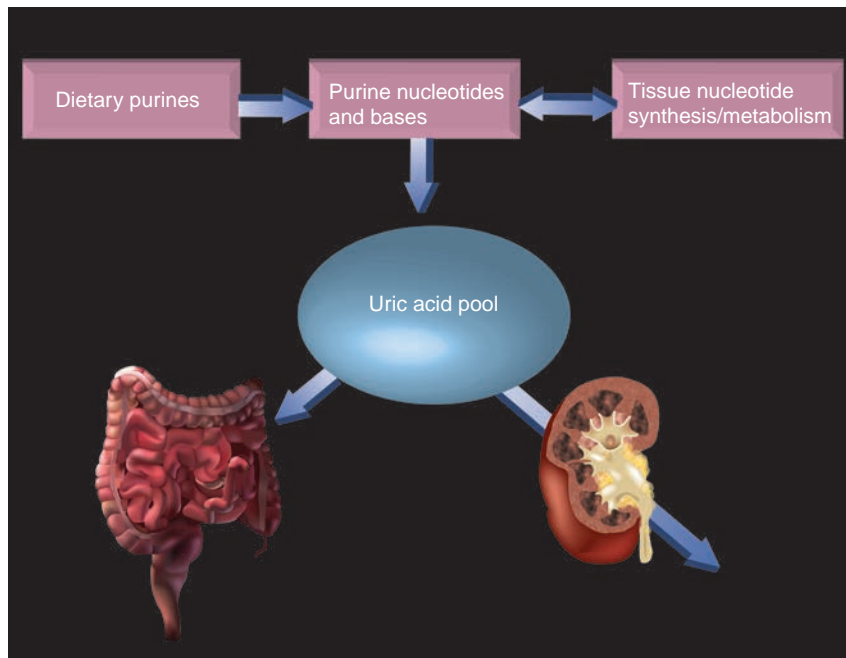


Figure 1. Simplified diagram of uric acid production and excretion.

Approximately two-thirds of the urate pool derives from endogenous production and a third from the diet. Approximately two-thirds of excretion is via the kidney and a third via the gut.

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14.8 vs 17.0). Lower SUA levels in women than men have been attributed to lower renal post-secretory reabsorption of uric acid, leading the authors to postulate that longer estrogen receptor gene thymine–adenine repeats facilitate uric acid excretion.

A major recent step forward in our understanding of the pathogenesis of gout has been the elucidation of various renal tubular urate transporters. The best characterized of these is URAT1 [13].

Box 1. Gout: risk factors and comorbid associations.

- Male gender
- Genetic predisposition
- Alcohol consumption
- Dietary factors
 - Animal purines (meat and seafood)
 - Sugar-sweetened soft drinks and fructose
- Hypertension
- Metabolic syndrome
 - Obesity
 - Hyperlipidemia
 - Insulin resistance
 - Cardiovascular risk
- Diuretics
- Renal disease
- Osteoarthritis

URAT1 is a 555 amino acid protein located in the luminal epithelium in the proximal tubule. It is encoded by the *SLC22A12* gene on chromosome 11q13 and is constituted by 2642 base pairs in 10 exons. The uricosuric effects of benzbromarone, sulfinpyrazone, probenecid and losartan, and urate-retaining properties of pyrazinamide and organic anions such as lactate and nicotinate, appear to be mediated via URAT1 (FIGURE 2). The G774A mutation in the *SLC22A12* gene, which substitutes a stop codon for tryptophan, is associated with renal hypouricemia [13–15]. In a study that compared G774A genotypes and allelic frequencies between 185 Japanese male patients with gout and 980 healthy controls, 4.6% of controls were heterozygous for G774A, whereas none of the gout subjects carried the variant A allele [16], suggesting that the G774A mutation is protective against the development of gout. A further six polymorphisms in the *SLC22A12* gene were identified in a study of 69 Mexican patients with primary gout [17]. The most common variant was C850G, a missense mutation substituting glycine for arginine, which was seen in 11 patients and appeared to associate with both lower triglyceride and SUA levels.

Polymorphisms in genes encoding other renal urate transporters have also been identified. GLUT-9 is a glucose transporter protein encoded by *SLC2A9* on chromosome 4. A single nucleotide polymorphism (SNP), rs6855911, located within *SLC2A9*, has been shown to be associated with both hyperuricemia and gout [18,19]. GLUT-9 is highly expressed in the liver and distal renal tubule, suggesting that an influence on urate levels could also be exerted via hepatic glucose uptake and subsequent increased production of uric acid, in addition to an effect on renal uric acid excretion. However, GLUT-9 has recently been shown to play a key role in renal tubular urate reabsorption, regulating transport of intracellular urate from the renal tubular cell into the peritubular interstitium [20]. A patient with renal hypouricemia was subsequently found to have a missense mutation in *SLC2A9*, which reduced urate transport [20]. *SLC2A9* genotypes have also been shown to account for significant variance in SUA levels and to associate with gout in a number of different populations [21,22]. A genome-wide association study was undertaken in 7699 participants in the Framingham cohort and 4148 participants in the Rotterdam cohort and then replicated in 14,867 participants in the Atherosclerosis Risk in Communities study [23]. Several SNPs associated with hyperuricemia

Table 1. Risk estimates and 95% confidence intervals for risk factors and comorbidities of gout.

Study	Risk factor	Study details	Risk estimate	95% CI	Ref.
Genetic factors					
Taniguchi et al. (2005)	SLC22A12 G774A polymorphism	Cross-sectional hospital-based study: 185 gout patients, 980 healthy controls.	OR: 0.00	0.00–0.49	[16]
Chang et al. (2007)	TNF- α C-863A polymorphism	Cross-sectional hospital-based study: 106 gout patients, 159 healthy controls.	OR: 18.12	2.27–144.51	[30]
Chang et al. (2007)	TNF- α G-308A polymorphism	See above	OR: 0.51	0.05–4.96	[30]
Chang et al. (2008)	cGMP-dependent protein kinase II rs7688672 polymorphism	Genome-wide scan in a Taiwanese gout family case-control study: 148 subjects	OR: 2.89	1.19–7.02	[32]
Chang et al. (2008)	cGMP-dependent protein kinase II rs6837293 polymorphism	See above	OR: 2.72	1.12–6.64	[32]
Alcohol					
Choi et al. (2004)	Alcohol consumption	Health Professionals Follow-up Study: 47,150 male health professionals, 730 incident cases of gout	RR: 1.17 per 10 g increase in daily intake	1.11–1.22	[36]
Choi et al. (2004)	Beer	See above	RR: 1.49 per daily 12 ounce serving	1.32–1.70	[36]
Choi et al. (2004)	Spirits	See above	RR: 1.15 per drink per day	1.04–1.28	[36]
Choi et al. (2004)	Wine	See above	RR: 1.04 per daily 4 ounce serving	0.88–1.22	[36]
Dietary factors					
Choi et al. (2004)	Meat	Health Professionals Follow-up Study: 47,150 male health professionals, 730 incident cases of gout.	RR: 1.41, highest versus lowest quintile	1.07–1.86	[38]
Choi et al. (2004)	Seafood	See above	RR: 1.51, highest versus lowest quintile	1.17–1.95	[38]
Choi et al. (2004)	Purine-rich vegetables	See above	RR: 0.96, highest versus lowest quintile	0.74–1.24	[38]
Choi et al. (2004)	Dairy products	See above	RR: 0.56, highest versus lowest quintile	0.42–0.74	[38]
Choi et al. (2007)	Coffee	Health Professionals Follow-up Study: 45,869 male health professionals, 757 incident cases of gout	RR: 0.60, six cups per day versus none	0.41–0.88	[39]
Choi et al. (2008)	Sugar-sweetened soft drinks	Health Professionals Follow-up Study: 46,393 male health professionals, 755 incident cases of gout	RR: 1.85, two drinks per day versus <1 per month	1.08–3.16	[40]
Choi et al. (2008)	Fructose	See above	RR: 2.02, highest versus lowest quintile	1.49–2.75	[40]
Hypertension, obesity & the metabolic syndrome					
Choi et al. (2005)	Hypertension	Health Professionals Follow-up Study: 47,150 male health professionals, 730 incident gout cases	RR: 2.31	1.96–2.72	[43]
Mikulic et al. (2005)	–	UK-GPRD, case-control study. 63,105 gout cases	OR: 1.52	1.48–1.56	[2]

CI: Confidence interval; EULAR: European League Against Rheumatism; GPRD: General Practice Research Database; HR: Hazard ratio; IRR: Incidence rate ratio; MRFFIT: Multiple Risk Factor Intervention Trial; NCEP/ATP III: National Cholesterol Education Programme Adult Treatment Panel III; NHANES/II: Third National Health and Nutrition Examination Survey; OA: Osteoarthritis; OR: Odds ratio; RR: Relative risk.

Table 1. Risk estimates and 95% confidence intervals for risk factors and comorbidities of gout.

Study	Risk factor	Study details	Risk estimate	95% CI	Ref.
Choi et al. (2005)	Body mass index	See above	RR: 2.97, BMI \geq 35 versus BMI 21–22.9	1.73–5.10	[43]
Choi et al. (2005)	Waist:hip ratio	See above	RR: 1.82, highest versus lowest quintile	1.39–2.39	[43]
Choi et al. (2005)	Weight gain	See above	RR: 1.99	1.49–2.66	[43]
Choi et al. (2005)	Weight loss	See above	RR: 0.61	0.40–0.92	[43]
Choi et al. (2008)	Diabetes mellitus	Cohort nested within MRFIT: 11,351 men, 644 gout cases	RR: 1.34	1.09–1.64	[44]
Mikul et al. (2005)	–	See above	OR: 1.11	1.06–1.16	[2]
Choi et al. (2007)	Metabolic syndrome (NCEP/ATP III criteria)	NHANESIII: Cross-sectional study, 8807 participants, 223 gout cases	OR: 3.05	2.01–4.61	[45]
Janssens et al. (2003)	Cardiovascular disease	Primary care case–control study: 261 gout cases, 522 controls	IRR: 0.98	0.65–1.47	[48]
Mikul et al. (2006)	–	See above	OR: 1.75	1.70–1.79	[2]
Zhang et al. (2006)	–	EULAR gout task force, meta-analysis of three epidemiological studies	RR: 1.24	0.92–1.67	[49]
Krishnan et al. (2006)	Acute myocardial infarction	Cohort nested within MRFIT: 12,866 men, 1123 gout cases	OR: 1.26	1.14–1.40	[50]
Choi et al. (2007)	–	Health Professionals Follow-up Study: 51,297 male health professionals, 2773 gout cases	RR: 1.59	1.04–2.41	[52]
Krishnan et al. (2008)	Cardiovascular death	Cohort nested within MRFIT: 9105 men, 655 gout cases	HR: 1.35	1.06–1.72	[51]
Choi et al. (2007)	–	See above	RR: 1.38	1.15–1.66	[52]
Diuretics					
Choi et al. (2005)	–	See above	RR: 1.77	1.42–2.20	[43]
Janssens et al. (2006)	–	Primary care case–control study: 70 gout cases, 210 controls	IRR: 0.6	0.2–2.0	[55]
Mikul et al. (2005)	–	See above	OR: 1.72	1.67–1.76	[2]

CI: Confidence interval; EULAR: European League Against Rheumatism; GPRD: General Practice Research Database; HR: Hazard ratio; IRR: Incidence rate ratio; MRFIT: Multiple Risk Factor Intervention Trial; NCEP/ATP III: National Cholesterol Education Programme Adult Treatment Panel III; NHANESIII: Third National Health and Nutrition Examination Survey; OA: Osteoarthritis; OR: Odds ratio; RR: Relative risk.

Table 1. Risk estimates and 95% confidence intervals for risk factors and comorbidities of gout.

Study	Risk factor	Study details	Risk estimate	95% CI	Ref.
Renal disease					
Choi et al. (2005)	Chronic renal disease	See above	RR: 3.61	1.60–8.14	[43]
Mikuls et al. (2005)	–	See above	OR: 4.95	4.28–5.72	[2]
Mikuls et al. (2005)	Renal transplantation	See above	OR: 25.13	12.97–48.68	[2]
Mikuls et al. (2005)	Ciclosporin use	See above	OR: 7.93	5.97–10.54	[2]
Osteoarthritis					
Roddy et al. (2007)	Sites of acute gout and OA	164 gout subjects (5904 individual joints)	OR: 7.94	6.27–10.05	[61]
Roddy et al. (2008)	Nodal OA	Primary care case-control study: 164 gout cases, 656 controls.	OR: 1.29	0.64–2.61	[62]

CI: Confidence interval; EULAR: European League Against Rheumatism; GPRD: General Practice Research Database; HR: Hazard ratio; IRR: Incidence rate ratio; MRFIT: Multiple Risk Factor Intervention Trial; NCEP/ATP-III: National Cholesterol Education Programme Adult Treatment Panel III; NHANES/II: Third National Health and Nutrition Examination Survey; OA: Osteoarthritis; OR: Odds ratio; RR: Relative risk.

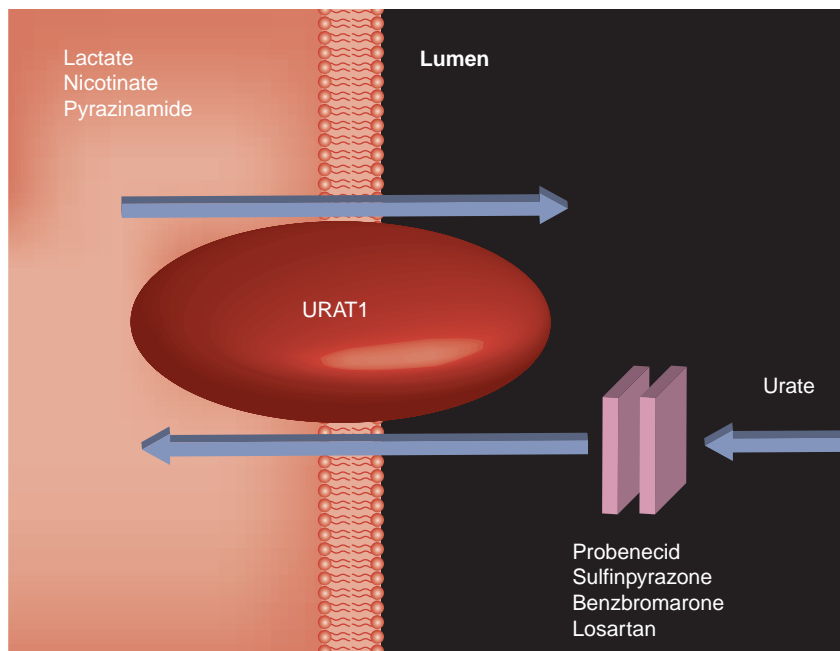


Figure 2. Schematic diagram showing transportation of organic anions across the renal tubular membrane and drug action at URAT1.

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and/or gout were identified. A missense SNP, rs16890979, in *SLC2A9* had a strong association with hyperuricemia and gout. Missense SNPs at two new loci encoding renal proximal tubule apical membrane transporters were identified: rs2231142 in *ABCG2*, a purine nucleoside transporter, and rs1165205 in *SLC17A3*, a sodium phosphate transporter, both of which were associated with gout.

There has also been recent interest in the role played by different cytokines in the development of gout. MSU crystals are specifically detected via the NALP3 inflammasome, an intracellular receptor within monocytes. Subsequent activation of the enzyme caspase-1 activates IL-1 β , initiating an inflammatory response [24,25]. IL-1 blockade with the IL-1 receptor antagonist, anakinra, has been shown to reduce MSU crystal-induced inflammation in an *in vivo* mouse model [26]. A pilot study of anakinra in ten patients with acute gout demonstrated rapid resolution in gout symptoms in all patients [26]. However, in a Taiwanese study of 196 patients with gout and 103 healthy controls, no associations were seen between gout and IL-1, IL-1 receptor antagonist, IL-4 or TNF- α -308 polymorphisms [27-29]. A second Taiwanese study found that the AA genotype at the TNF- α C-863A polymorphism was significantly associated with gout compared with the CC genotype (odds ratio [OR]: 18.12; 95% confidence interval [CI]: 2.27-144.51).

No association was seen between gout and the G-308A polymorphism [30]. TGF- β 1 is a cytokine that has a key role in downregulating the inflammatory response, and hence may play a role in terminating attacks of acute gout. A study from Taiwan compared polymorphisms in the *TGF- β 1* gene between 73 gout patients and 114 healthy controls [31]. Genotype and allele frequencies for the T869C and C-509T polymorphisms did not differ between gout patients and controls. However, within the group with gout, the TT genotype at polymorphism T869C was associated with both the presence of tophi (OR: 11.06; 95% CI: 1.84-66.36) and the total number of tophi (median 3.73 vs 0.35) when compared with the CC genotype. The authors postulate that the TT genotype leads to dysfunction of TGF- β 1, which in turn leads to incomplete termination of the inflammatory response to MSU crystals and hence tophus formation.

A recent study that undertook a genome-wide scan in a Taiwanese family affected by gout identified a locus on chromosome 4q21 that was significantly related to gout [32]. The same authors then performed SNP genotyping analysis in a case-control study of 148 subjects, identifying two polymorphisms located on the cGMP-dependent protein kinase II gene, rs7688672 (OR: 2.89; 95% CI: 1.19-7.02) and rs6837293 (OR: 2.72; 95% CI: 1.12-6.64), which were significantly associated with gout in a recessive model after adjustment for hyperuricemia.

Polymorphisms in the α 2-adrenoceptor [33], β 3-adrenergic receptor [34] and methylene tetrahydrofolate reductase [35] genes have been found to associate with hyperuricemia but, to date, their relationship to gout has not been studied. Potential associations between these polymorphisms and gout are worthy of further study.

Alcohol & dietary factors

Historically, gout has long been associated with rich-living and excessive consumption of alcohol and dietary purines. However, it is only recently that robust prospective epidemiological evidence has emerged that excess alcohol consumption and dietary factors are independent risk factors for the development of gout. The Health Professionals Follow-up Study followed 47,150 male health professionals (dentists, optometrists, osteopaths, veterinarians, pharmacists and podiatrists) prospectively over a 12-year period, observing 730 incident cases of gout [36]. Incident gout was independently associated with alcohol consumption (multivariate relative risk

[RR]: 1.17 per 10 g increase in daily intake; 95% CI: 1.11–1.22) after adjustment for confounding variables. Consumption of beer conferred the greatest degree of risk (RR: 1.49 per 12 ounce serving per day; 95% CI: 1.32–1.70) followed by spirits (RR: 1.15 per drink/shot per day; 95% CI: 1.04–1.28), whereas moderate wine consumption conferred no risk (RR: 1.04 per 4 ounce serving per day; 95% CI: 0.88–1.22). Beer is rich in the purine, guanosine, which is a substrate for urate whereas wine contains antioxidants and vasorelaxants. Alcohol consumption has also been shown to be an important trigger of recurrent acute attacks of gout. An internet crossover study of 321 attacks of acute gout affecting 197 participants found a dose–response relationship between the risk of a recurrent attack of acute gout and the number of alcoholic drinks consumed in the preceding 48 h (seven alcoholic drinks in 48 h: OR: 2.5; 95% CI: 1.1–5.9) after adjustment for purine intake and diuretic use [37].

Recent studies of the role played by diet in the development of gout have focused not only on purines but on other dietary factors also. In the Health Professionals Follow-up Study, high levels of consumption of meat (RR highest vs lowest quintile: 1.41; 95% CI: 1.07–1.86) and seafood (RR: 1.51; 95% CI: 1.17–1.95) were independent risk factors for the development of gout after adjustment for important confounders [38]. Interestingly, consumption of purine-rich vegetables was not associated with the development of gout (RR: 0.96; 95% CI: 0.74–1.24). The incidence of gout demonstrated an inverse relationship with intake of dairy products (RR highest vs lowest quintile: 0.56; 95% CI: 0.42–0.74), although this inverse relationship was confined to low-fat dairy products (RR: 0.58; 95% CI: 0.45–0.76), but not those high in fat (RR: 1.00; 95% CI: 0.77–1.29).

Further analyses from this cohort have examined the role of other dietary factors in the development of gout. An inverse relationship between coffee consumption and incident gout has been observed [39]. The multivariate RR of gout in those drinking at least six cups of coffee per day was 0.60 (95% CI: 0.41–0.88), compared with those who did not drink coffee after adjustment for consumption of meat, seafood, dairy products and vitamin C. Evidence of a similar trend for consumption of decaffeinated coffee was seen, although RR in the most exposed group did not reach statistical significance (RR: 0.73; 95% CI: 0.46–1.17). There was no association

between incident gout and either tea consumption (RR: 0.82; 95% CI: 0.38–1.75) or total caffeine intake (RR highest vs lowest quintile: 0.83; 95% CI: 0.64–1.08). A number of mechanisms have been postulated to explain a link between coffee consumption and the risk of incident gout. The trend observed for decaffeinated coffee and the lack of association with either tea consumption or total caffeine intake suggest that the protective effect of caffeine is attributable to noncaffeine coffee constituents. Most recently, consumption of sugar-sweetened soft drinks and fructose have been shown to be independent risk factors for the development of gout [40]. The multivariate RR of gout in those drinking at least two sugar-sweetened soft-drinks per day was 1.85 (95% CI: 1.08–3.16), compared with those who drank fewer than one drink per month after adjustment for body mass index (BMI) and other dietary factors. However, this association became insignificant after adjustment for fructose intake also. Consumption of diet soft drinks was not associated with the development of gout (RR: 1.12; 95% CI: 0.82–1.52). Fructose intake was associated with the development of gout (RR highest vs lowest quintile: 2.02; 95% CI: 1.49–2.75), again adjusting for important confounders. Consumption of various fructose-containing foods including fruit juices, oranges and apples were also associated with gout. Fructose consumption is thought to predispose to hyperuricemia by increasing nucleotide turnover by degradation of ATP to AMP, and hence enhancing substrate provision, a mechanism by which alcohol also predisposes to hyperuricemia.

Finally, there has also been interest in vitamin C, which has uricosuric properties, as a dietary factor that might be linked to hyperuricemia and gout. An analysis from a subsample of the Health Professionals Follow-up Study has shown an inverse dose–response relationship between SUA levels and intake of vitamin C [41]. This subsample consisted of 1387 nonobese men without hypertension. Significant inverse trends were seen between SUA levels and both total vitamin C intake and consumption of vitamin C supplements. Multivariate OR for hyperuricemia in those consuming greater than 1000 mg of vitamin C daily was 0.34 (95% CI: 0.17–0.56) compared with the referent group (those consuming less than 90 mg per day). These findings are supported by the findings of a double-blind, placebo-controlled, randomized control trial that randomized 184 nonsmokers to take

either vitamin C supplements of 500 mg daily or placebo [42]. Over a 2-month period, a mean reduction in SUA of 0.5 mg/dl was seen in the vitamin C group compared with no change in the placebo group. However, these observations are confined to vitamin C and SUA levels. To date, a possible relationship between vitamin C and gout has not been studied, although it seems likely that a similar association exists.

Hypertension, obesity & the metabolic syndrome

Gout is associated with considerable medical comorbidity including hypertension, obesity, hyperlipidemia, insulin resistance and cardiovascular disease – features of the metabolic syndrome. Several studies have examined different components of the metabolic syndrome. In the Health Professionals Follow-up Study, hypertension was an independent risk factor for the development of gout after adjustment for diuretic therapy (RR: 2.31; 95% CI: 1.96–2.72) [43]. An important dose–response relationship between BMI and incident gout was also identified (BMI: <21, RR: 0.85; BMI: 21–22.9, RR: 1.00 [referent]; BMI: 23–24.9, RR: 1.31; BMI: 25–29.9, RR: 1.95; BMI: 30–34.9, RR: 2.33; BMI: >35, RR: 2.97). Similar relationships were seen for waist:hip ratio and weight gain. Weight loss since study baseline appeared to be protective against gout. A large case–control study undertaken in the UK-General Practice Research Database (UK-GPRD) compared 56,483 patients with gout to 150,867 control subjects with osteoarthritis (OA) [2]. After adjustment for age and gender, gout was associated with both hypertension (OR: 1.52, 95% CI: 1.48–1.56) and diabetes mellitus (OR: 1.11, 95% CI: 1.06–1.16). Gout has also been shown prospectively to be associated with an increased risk of developing Type II diabetes mellitus. In a prospective cohort study nested within the Multiple Risk Factor Intervention Trial (MRFIT), 11,351 men with a high cardiovascular risk profile were followed over a 6-year period [44]. The multivariate RR of incident Type II diabetes mellitus in those with a history of gout at baseline was 1.34 (95% CI: 1.09–1.64) compared with those without gout after adjustment for components of the metabolic syndrome, physical activity and dietary factors. These studies have examined different components of the metabolic syndrome, yet a further epidemiological study has considered the prevalence of the metabolic syndrome

in patients with gout. Using data collected during the Third National Health and Nutrition Examination Survey (NHANES-III), the prevalence of the metabolic syndrome defined according to the National Cholesterol Education Programme Adult Treatment Panel III (NCEP/ATP III) criteria was compared between 223 subjects with gout and 8584 control subjects [45]. The metabolic syndrome was present in 62.8% of subjects with gout and 25.4% of control subjects (OR: 3.05; 95% CI: 2.01–4.61; adjusted for age and gender). Individual components of the metabolic syndrome associated with gout were abdominal obesity, hypertriglyceridemia, low high-density lipoprotein cholesterol, hypertension and insulin resistance. It is thought that insulin resistance is the major mediator of hyperuricemia in the metabolic syndrome [46], although hypertension also exerts renal vascular effects that predispose to hyperuricemia [47].

The association of individual metabolic syndrome components with gout and the high prevalence of the metabolic syndrome in patients with gout imply that gout is associated with significant cardiovascular risk. There has been much debate as to whether gout is an independent risk factor for cardiovascular disease – that is, whether gout confers additional risk beyond its co-association with traditional cardiovascular risk factors. A cohort study undertaken in four Dutch general practices compared incident cardiovascular disease over a mean follow-up period of 11.1 years in 170 patients presenting with their first attack of gout, and 340 age- and gender-matched control subjects; both groups were without known cardiovascular disease [48]. Cardiovascular disease developed in 26% of the gout patients and 21% of control subjects, but gout was not found to be an independent predictor (risk ratio: 0.98; 95% CI: 0.65–1.47). A subsequent analysis by the European League Against Rheumatism (EULAR) Gout Task Force pooled the results of this study with the results of two earlier cohort studies, but did not find evidence of an independent contribution of gout to cardiovascular disease (pooled RR: 1.24; 95% CI: 0.92–1.67) [49]. More recent larger epidemiological studies have suggested that gout might make an independent contribution to cardiovascular risk. In the UK-GPRD study, gout was significantly associated with coronary artery disease after adjustment for age and gender, but risk estimates were not adjusted for traditional cardiovascular risk factors (OR: 1.75; 95% CI: 1.70–1.79) [2]. Two prospective cohort analyses of incident

cardiovascular disease have been undertaken in the MRFIT dataset. In the first analysis, 12,866 men with a high cardiovascular risk profile were followed for 6 years, 1123 reporting gouty arthritis during the study period [50]. Gout was an independent risk factor for acute myocardial infarction after adjustment for traditional cardiovascular risk factors (OR: 1.26; 95% CI: 1.14–1.40). The second analysis followed 9105 men with the same cardiovascular risk profile over a 17-year period, with a primary end point of cardiovascular disease mortality [51]. The multivariate hazard ratio (HR) for cardiovascular disease mortality between patients with and without gout was 1.35 (95% CI: 1.06–1.72). Further evidence of the independent contribution of gout to the risk of cardiovascular death comes from the Health Professionals Follow-up Study. Amongst men without coronary heart disease at baseline, gout was an independent risk factor for incident cardiovascular death (RR 1.38; 95% CI: 1.15–1.66), fatal coronary heart disease (RR: 1.55; 95% CI: 1.24–1.93) and non-fatal myocardial infarction (RR: 1.59; 95% CI: 1.04–2.41) [52].

In summary, gout is associated with the metabolic syndrome. Hypertension and obesity are independent risk factors for the development of gout, whereas gout predicts the onset of Type II diabetes mellitus. Gout is also associated with cardiovascular disease, with recent studies suggesting that it makes an independent contribution to cardiovascular risk. Based on the significant cardiovascular burden experienced by patients with gout, recent evidence-based recommendations for the diagnosis and management of gout advocate screening patients with gout for the presence of cardiovascular risk factors [49,53,54].

Diuretics

Diuretic use is frequently associated with gout in clinical practice, particularly in the elderly and in the presence of cardiovascular and renal disease. In the Health Professionals Follow-up Study, diuretic use was an independent risk factor for the development of gout (RR: 1.77; 95% CI: 1.42–2.20) after adjustment for hypertension and renal disease [43]. Similarly, in the UK-GPRD study, gout was associated with diuretic use (OR: 1.72; 95% CI: 1.67–1.76) although adjustment was made for age and gender only, but not comorbidity [2]. In contrast, in the Dutch case–control study described above, no association between diuretic use of greater than 3-months duration and gout was found (incidence rate ratio:

0.6; 95% CI: 0.2–2.0; adjusted for hypertension, heart failure and myocardial infarction), although the number of cases was smaller ($n = 70$) than other studies and several important confounding variables were not included in the multivariate analysis – for example, obesity, alcohol, dietary factors and renal disease [55]. Diuretic use also increases the risk of recurrent attacks of acute gout. In the internet-based case crossover study described above [37], the occurrence of an acute attack of gout was associated with use of any diuretic over the previous 48 h (OR: 3.6; 95% CI: 1.4–9.7) adjusting for purine and alcohol intake [56]. This suggests that diuretics are a significant contributor to persistent clinically significant symptomatic gout.

A number of renal tubular organic anion transporters (OATs) have been shown to regulate tubular urate handling and be targeted by diuretics potentially leading to hyperuricemia [13,57,58]. It is thought that the entry of diuretics into the renal tubular cell occurs via basolateral OATs, the entry of thiazide and loop diuretics being mediated principally by OAT1 and OAT3, respectively [58]. Intracellular diuretics then act as anions at apical membrane OATs, which facilitate the transport of diuretics into the urine in exchange for urate. URAT1 has been shown to interact with the loop diuretics, bumetanide and furosemide [13]. Reabsorption of urate from the renal tubular lumen by OAT4 is increased by intracellular hydrochlorothiazide [57]. OAT4 may also play a role in the excretion of bumetanide [58].

Renal disease

Chronic renal disease is an important risk factor for the development of gout, and was associated with gout in both the Health Professionals Follow-up Study (RR 3.61; 95% CI: 1.60–8.14) [43] and the UK-GPRD study (OR: 4.95; 95% CI: 4.28–5.72) [2]. This relationship has the potential for confounding by multiple variables, including diuretic therapy and hypertension. In addition to including these variables in their multivariate analysis, the Health Professionals Follow-up Study repeated this analysis in men without diuretic exposure, finding a similar degree of risk (RR: 4.60; 95% CI: 1.88–11.25) [43]. Gout can be particularly problematical in patients with end-stage renal disease treated with hemodialysis and in renal transplant recipients. A study of 259,209 patients in the United States Renal Data System found the incidence of gout to be 5% in the first year of dialysis and 15.4%

in the first 5 years [59]. Incident gout was also an independent predictor of mortality (HR: 1.49; 95% CI: 1.43–1.55). Gout frequently complicates renal transplantation (OR: 25.13; 95% CI: 12.97–48.68) [2]; hyperuricemia following renal transplantation could plausibly occur via several mechanisms, including diuretic therapy, hypertension, allograft dysfunction and immunosuppressive therapy with ciclosporin, which reduces renal urate clearance. In a study of 202 renal transplant recipients from New Zealand, use of a loop diuretic post-transplant and renal impairment were more frequent in gout sufferers than age- and gender-matched control subjects without gout [60]. However, the number prescribed ciclosporin and the dose of ciclosporin did not differ between the groups. In contrast, in the UK-GPRD study, ciclosporin use was strongly associated with gout (OR: 7.93; 95% CI: 5.97–10.54), although this analysis was not specific to renal transplant recipients [2].

Osteoarthritis

Hyperuricemia is considered to be the primary risk factor for the development of gout, yet most hyperuricemic individuals do not develop gout, even amongst individuals with the highest SUA levels. Gout typically presents in a very characteristic manner, showing a marked predilection for the first metatarsophalangeal (MTP) joint,

which is also a target site for OA. It has been postulated that the readiness of MSU crystals to deposit in osteoarthritic cartilage might explain both of these common observations.

Several case reports and small case series describe the occurrence of acute gout and/or tophi at joints affected by OA. More recently, a community-based study of 164 patients with gout showed a strong association between the sites of acute attacks of gout and the presence of clinically-defined osteoarthritis (adjusted OR: 7.94; 95% CI: 6.27–10.05), particularly at the first MTP joint, mid-foot, knee and finger distal interphalangeal joints [61]. The cross-sectional nature of this study does not readily differentiate whether OA predisposes to local crystal deposition or joint damage arises from crystal deposition. However, the association between joints affected by gout and OA was not influenced by gout duration, which does not support the latter hypothesis. It is also possible that generalized OA might be a risk factor for the development of gout. A case-control study comparing the same group of 164 gout cases with age- and sex-matched controls derived from the same community found that nodal OA was not associated with gout, suggesting that OA is not a risk factor for the development of gout *per se* [62]. However, knee pain, big toe pain and hallux valgus were more prevalent in gout cases

Executive summary

Genetic factors

- Several renal tubular urate transporters have been identified. Polymorphisms in genes encoding these transporters influence the risk of developing gout.
- *TNF- α* gene polymorphisms associate with the development of gout.
- Tophus formation is associated with *TGF- β 1* gene polymorphisms.

Alcohol & dietary factors

- Alcohol consumption is an independent risk factor for the development of gout.
- Beer confers the greatest risk, followed by spirits, whereas moderate wine consumption contributes little risk.
- Diets rich in animal purines (meat and seafood), fructose and sugar-sweetened soft drinks are independent risk factors for the development of gout.
- Dairy products, coffee and vitamin C appear to reduce the risk of developing gout.

Hypertension, obesity & the metabolic syndrome

- There is a strong association between gout and hypertension, obesity, insulin resistance and the metabolic syndrome.
- An independent association between gout and cardiovascular disease remains controversial, although the most recent epidemiological studies suggest an independent contribution of gout to cardiovascular risk.

Diuretics

- Diuretic use is an independent risk factor for the development of gout.
- The urate-retaining properties of diuretics are exerted via the renal tubular organic anion transporters.

Renal disease

- Chronic renal disease is frequently associated with challenging gout, particularly amongst transplant recipients.

Osteoarthritis

- Osteoarthritis predisposes to local crystal deposition at individual joint sites, but is not a risk factor for the development of gout *per se*.

than control subjects, supporting the suggestion that OA predisposes to local crystal deposition at individual joint sites.

Further evidence of an association between gout and OA comes from a recent cadaveric study [63]. A total of 7855 adult human tali from 4007 donors were examined for macroscopic and microscopic evidence of crystal deposition (both MSU and calcium pyrophosphate dihydrate crystals) and cartilage degeneration. Crystal-positive specimens displayed cartilage degeneration more frequently than crystal-negative specimens (54.7 vs 26.0%) and had a higher mean grade of gross cartilage degeneration. Co-localization of crystal deposits and cartilage lesions appeared to occur at sites of greatest adverse biomechanical stress.

Conclusion

Over recent years, there has been a considerable increase in our understanding of factors predisposing to gout. A major step forward has been the elucidation of renal tubular organic anion transporters. The process of unraveling the complexity of genetic susceptibility to gout has begun with the identification of potentially important polymorphisms in genes encoding both renal urate transporters and key cytokines regulating the inflammatory response to MSU crystals. Epidemiological studies have confirmed both long-recognized associations with lifestyle factors such as alcohol, diet and obesity, and the strong association with comorbidity, which translates into significant cardiovascular risk.

Future perspective

Over the next decade, a better understanding of the pathophysiology and molecular biology of hyperuricemia and gout will undoubtedly evolve, with the renal basis for hyperuricemia and renal tubular urate transport likely to be at the forefront of this revolution. Increasing numbers of genetic markers for gout will be identified, which may predict clinical presentation, disease severity and treatment response and/or toxicity, in addition to the risk of developing the disease. Interactions between genes and other predisposing or comorbid factors, for example, lifestyle factors, are also likely to be of interest. What is known about factors predisposing to gout mostly concerns risk factors for hyperuricemia. Less is known about risk factors for crystal formation and deposition, although recent observations concerning gout and osteoarthritis, and the genetic basis for the inflammatory response to monosodium urate crystals, may reawaken interest in this area.

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