

Epidemiology of Hyperuricemia and Gout

Andrew J. Luk, MD, MPH; and Peter A. Simkin, MD

Abstract

Gout is an increasingly common medical problem. The traditional risk factors of male sex and high red meat or alcohol consumption have been joined by a wave of newer risk factors, such as increased longevity, the metabolic syndrome (hypertension, diabetes, dyslipidemia, truncal obesity, increased cardiovascular disease risk), use of diuretics, low-dose aspirin, or cyclosporine, and end-stage renal disease. Atypical presentations of gout in the elderly can mimic osteoarthritis and rheumatoid arthritis. There is a resurgence of interest in hyperuricemia as an independent and potentially modifiable cardiovascular risk factor. The pharmacologic management of gout in general practice suffers from a number of quality-control issues. This article reviews these and other new epidemiologic data on this ancient disease.

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When the blood level of urate, the end-product of purine metabolism, reaches its physiologic limit of solubility, it may crystallize into monosodium urate (MSU) in the tissues and cause gout. Gout affects at least 1% of the population in Western countries and is the most common inflammatory joint disease in men older than 40 years of age.^{1,2}

The clinical spectrum ranges from the classic presentation of episodic, acute inflammation of the first metatarsophalangeal joint (ie, podagra) to tophaceous gout, chronic polyarticular arthritis, urate nephrolithiasis, and interstitial nephropathy. Historically a disease of affluent, middle-aged or older men with overindulgent lifestyles, gout has now become more “democratic” by affecting more women and a wider range of socioeconomic groups.

The worldwide incidence and prevalence of gout appear to be increasing for a variety of reasons, including iatrogenic ones. New dietary data confirm the long-held associa-

tion of gout with high meat or alcohol intake, but not with high-purine vegetables. Hyperuricemia, the predisposing condition for gout, is intricately linked with the metabolic syndrome (hypertension, glucose intolerance, dyslipidemia, truncal obesity, increased risk of cardiovascular disease), and there is mounting evidence that hyperuricemia itself may be an independent risk factor for cardiovascular disease. Unfortunately, gout is frequently mismanaged, resulting in unnecessary morbidity and even mortality.

Risk Factors for Hyperuricemia and Gout

Hyperuricemia, usually defined as a serum urate (SU) level >7 mg/dL, may be present in up to 18% of some populations.³ Hyperuricemia can be caused by overproduction of urate, or, far more commonly, by inefficient excretion by the kidneys. Diseases associated with overproduction include acquired conditions of high cellular turnover (eg, myeloproliferative disorders, some lymphomas, and exfoliative psoriasis), genetic errors (eg, deficient hypoxanthine-guanine phosphoribosyl transferase), and the rare, but potentially catastrophic, tumor lysis syndrome. Together, these account for <10% of cases of hyperuricemia in the general population. Inefficient excretion of uric acid, which accounts for >90% of cases, can be the result of renal insufficiency of any cause, or medications that impair renal urate clearance. SU levels may also increase with aging and weight gain.^{4,6} At least two thirds of patients with hyperuricemia can be expected to remain asymptomatic, and current evidence does not support treating asymptomatic hyperuricemia.⁷⁻¹¹

Widely used medications that can cause hyperuricemia by decreasing renal urate excretion are thiazides or loop diuretics and

low-dose aspirin. Other offending medications include cyclosporine A, antituberculous antibiotics (pyrazinamide and ethambutol), niacin, and didanosine.¹² Approximately 80% of transplant patients receiving cyclosporine have hyperuricemia, which is often marked (>12 mg/dL). Gout develops in >10% of patients within a few years of transplant and is characteristically severe and polyarticular.¹³⁻¹⁵ Cyclosporine probably induces hyperuricemia via multiple mechanisms, including decreasing renal tubular excretion of urate, declining glomerular filtration rate, and drug-induced interstitial nephropathy.

Dietary factors that contribute to hyperuricemia include high alcohol intake (which increases purine production and decreases urate excretion) and consumption of purine-rich foods, such as red meat or seafood.^{16,17} Fructose is a widely prevalent dietary constituent of special interest. Although it is not a purine, it causes hyperuricemia by accelerating the catabolism of adenine nucleotides. A recent study found that ingestion of 5 apples caused a 35% increase in the SU level within 6 hours after consumption.¹⁸

Hyperuricemia is also closely allied with the metabolic syndrome and its individual components, an association that seems to be independent of potential confounders, such as diuretic use and renal insufficiency.¹⁹⁻²⁴ Hypertension, diuretic use, high alcohol intake, and obesity contribute to the risk of developing gout in an additive manner.^{7,25,26}

Multiple genes regulate SU levels. Hyperuricemia and gout are particularly common in Filipinos, Samoans, Maori, and other South Pacific Islanders, probably because of the combination of a high seafood diet and poorly defined genetic differences in the excretion of uric acid.²⁷ Filipinos who emigrate to North America experience a rise in SU levels and further increase their risk of gout, likely owing in part to the shift to a Western diet.²⁸ African Americans have more hyperuricemia and gout than European Americans, probably reflecting their higher rates of hypertension, obesity, and end-stage renal disease.²⁹

Men have a greater risk of developing

gout than women in all age groups, although the sex ratio tends to equalize with advancing age. In the National Health and Nutrition Examination Survey III, the overall men:women ratio ranged between 7:1 and 9:1.³⁰ In a managed care population in the United States, the sex ratio among patients with gout was 4:1 in those younger than 65 years, and 3:1 in those older than 65 years.³¹ Fifty percent of patients older than 60 years with newly diagnosed gout are women, and the proportion may exceed 50% in those older than 80 years.^{4,32} Young children of both sexes have equally low urate levels, but among adults, men have higher SU levels than women. It seems obvious that this difference is of endocrine origin, but the precise mechanism has not been established. After menopause, women's SU values rise to levels comparable with those of men of the same age, although hormone replacement therapy may attenuate this rise. Postmenopausal women, especially those receiving diuretics, may develop gouty arthritis and tophi in the Heberden's and Bouchard's nodes of their osteoarthritic hands.³³ Elderly patients with unrecognized gout may progress insidiously to a symmetric, polyarticular, inflammatory disease that mimics rheumatoid arthritis, complete with "nodules" that are actually tophi.

The risk of developing gout is directly related to the degree of hyperuricemia. In a prospective study, the annual incidence of gout (ie, the proportion of new gout cases diagnosed per year in an at-risk population) was 0.1% in men whose SU levels were <7 mg/dL, 0.5% for levels between 7.0 and 8.9 mg/dL, and 4.9% for levels >9.0 mg/dL.⁷ In another study, the 5-year prevalence of gout (ie, the proportion of patients with gout in a given population over the specified period of time) was 0.6% in patients with urate levels <7 mg/dL, but 30% in patients with levels >10 mg/dL.³²

A lengthy period of asymptomatic hyperuricemia often precedes the first attack of gouty arthritis, and an even longer period may be required for tophi to form. After their first attack, however, most untreated patients will experience a second episode within 2 years.³⁴

The Changing Prevalence and Incidence of Gout

Comparing epidemiologic studies of gout is complicated by the lack of a standard case definition for gout (eg, self-reported vs physician-diagnosed), varying methods of calculating prevalence and incidence, and the different populations studied. For example, relying on self-reports likely overestimates the true prevalence and incidence. The American College of Rheumatology (ACR) Classification Criteria for gout have not been well-validated in different populations, and confirming the diagnosis by arthrocentesis to demonstrate the presence of MSU crystals in synovial fluid or tophi is not practical at the population level.³⁵

Nevertheless, a recent review of studies from Western countries suggests that both the prevalence and incidence of gout have been increasing over the past 4 decades.³⁶ The **Table** summarizes these incidence and prevalence studies. Two studies in the United Kingdom, one in the 1970s and the other in 1993, showed that overall gout prevalence increased from 0.26% to 0.95%.^{37,38} In a US managed care population, the prevalence of gout in a population aged older than 75 years (ascertained by pharmacy claims for gout medications) doubled from 2.1% to 4.1% between 1990 and 1999.³⁰ In the National Health Interview Survey, the overall prevalence of self-reported gout rose from 0.5% in 1969 to 0.9% in 1996.^{39,40} In New Zealand, the gout prevalence in Maori men rose from 4.5% in 1956 to 13.9% in 1992, and from 0.7% to 5.8% in European men.⁴¹ The prevalence may also be increasing in developing countries in the Far East.^{42,43}

Unlike prevalence, determining incidence requires long-term, prospective cohort studies, so few incidence data are available. In the United Kingdom, the General Practitioner Research Database yielded a gout incidence of about 14 per 10 000 person-years in 1990-1999, which remained relatively stable over that period.⁴⁴ By comparison, male veterans in the United States had a higher overall incidence of 28 per 10 000 patient-years between 1963 and 1978, probably reflecting the greater age, and higher prevalence of metabolic syn-

drome, diuretic use, renal insufficiency, and other risk factors in that population.⁷ The Rochester Epidemiology Project database showed that the age- and sex-adjusted incidence of acute gout (diagnosed by ACR Classification Criteria) increased from 4.5 to 6.2 per 10 000 person-years during the 10-year interval from 1977-1978 to 1986-1987, whereas the incidence of primary gout (ie, gout developing in patients not taking diuretics) more than doubled from 2.0 to 4.6 per 10 000 person-years during that period.⁴⁵ In this cohort, there was no increase in the incidence of metabolic syndrome or diuretic-related gout; therefore, the increase in the incidence of primary gout was attributed in part to greater physician recognition of atypical cases.

A number of factors have been proposed to explain the increasing prevalence of gout in the United States. This increase may be a result of increased longevity, because prevalence is a function of both disease incidence and disease duration. Other contributing factors may be the increased prevalence of hypertension and metabolic syndrome, increased use of diuretics and low-dose aspirin, dietary trends, change in demographics (eg, increased African American and Hispanic populations, in which the metabolic syndrome is more common), increased prevalence of end-stage renal disease, and increases in organ transplantation.³⁶

Gout, the Metabolic Syndrome, and Cardiovascular Risk

Up to 76% of patients with gout have the metabolic syndrome.^{46,47} Hyperuricemia is related to the individual components of the metabolic syndrome in complex ways. Hypertension itself can induce hyperuricemia, possibly because the decreased renal blood flow increases urate reabsorption.⁴⁸ Conversely, experimentally induced hyperuricemia (>2 mg/dL) in rats causes hypertension and vascular injury, which can then be reversed by lowering urate levels with the xanthine oxidase inhibitor allopurinol.⁴⁹ Hyperuricemia in childhood was found to be associated with hypertension that persists into adulthood.⁵⁰ According to one theory, the loss of uricase (which

Table. Increased Gout in the Overall Adult Population in Western Industrialized Countries Over the Past 4 Decades as Evaluated by Different Survey Approaches

Author/study (ref)	Year	Population	Gout statistics
Currie (Ref 37)	1978	Great Britain	Prevalence 2.6/1000 (physician diagnosis)
Harris, et al (Ref 38)	1995	Great Britain	Prevalence 9.5/1000 (physician diagnosis)
Klemp, et al (Ref 41)	1956-1966	New Zealand	Prevalence 7-20/1000 (in Caucasians, ACR criteria)
	1992	New Zealand	Prevalence 58/1000
National Arthritis Data Workgroup (Ref 39)	1969	US	Prevalence 5/1000 (self-report)
National Health Interview Survey (Ref 40)	1996	US	Prevalence 9.4/1000 (self-report)
Wallace, et al (Ref 31)	1990	US	Prevalence 2.1/1000 (age >75 years, drug codes)
	1999	US	Prevalence 4.1/1000 (age >75 years)
Mikuls, et al (Ref 44)	1990-1999	Great Britain	Incidence 14/10 000 patient-years (physician diagnosis, drug codes)
Campion, et al (Ref 7)	1963-1978	US veterans	Incidence 14/10 000 patient-years (physician diagnosis, drug codes)
Arromdee, et al (Ref 45)	1977-1978	US (Rochester, MN)	Incidence 4.5/10 000 patient-years (ACR criteria)
	1995-1996	US (Rochester, MN)	Incidence 6.2/10 000 patient-years

ACR indicates American College of Rheumatology. Adapted from Reference 36.

breaks down uric acid) during the evolution of African hominids may have conserved sodium and increased blood pressure in response to an upright posture.⁵¹ Alternatively, urate, an effective antioxidant, may have been retained to replace the antioxidant properties of vitamin C, which hominids lost the ability to synthesize at about the same time.⁵²

Hyperuricemia is probably associated with glucose intolerance via multiple mechanisms, but the central one may be the enhancing effect of insulin resistance on renal urate absorption.⁴⁷ Increased body mass index is also directly correlated with hyperuricemia, and leptin may be a contributory factor.⁵³ Higher adiposity and weight gain are strong risk factors for gout, whereas weight loss is protective.^{5,6,54} Dyslipidemia may induce hyperuricemia through its negative effect on renal function.⁵⁵

Hyperuricemia has long been suspected to be a cardiovascular risk factor. Although the Framingham Heart Study found no independent association between hyperuricemia and increased risk of coronary artery disease, several subsequent studies have found

one.⁵⁶⁻⁵⁹ A recent review concluded that SU is a moderate, independent cardiovascular risk factor, and appears to be a stronger risk factor in individuals already at high risk for cardiovascular disease than in healthy individuals. The authors therefore proposed a trial of urate-lowering therapy in high-risk patients to determine whether this improves cardiovascular outcomes.⁶⁰ Hyperuricemia was a poor prognostic factor in patients with congestive heart failure, and allopurinol treatment may improve outcomes.^{61,62} In a clinical trial, the angiotensin receptor blocker losartan (which has uricosuric properties) was shown to improve cardiovascular outcomes, and it was estimated that 29% of the treatment effect was because of lowering SU.⁶³ Despite all these data, it is still not completely clear if there is an independent association between hyperuricemia and cardiovascular risk in adults, or if hyperuricemia is merely a marker for those at risk.

Gout and Diet: New Insights

Gout and diet were explored in a prospective study of 47 150 men in the Health Professionals Follow-up Study between 1986

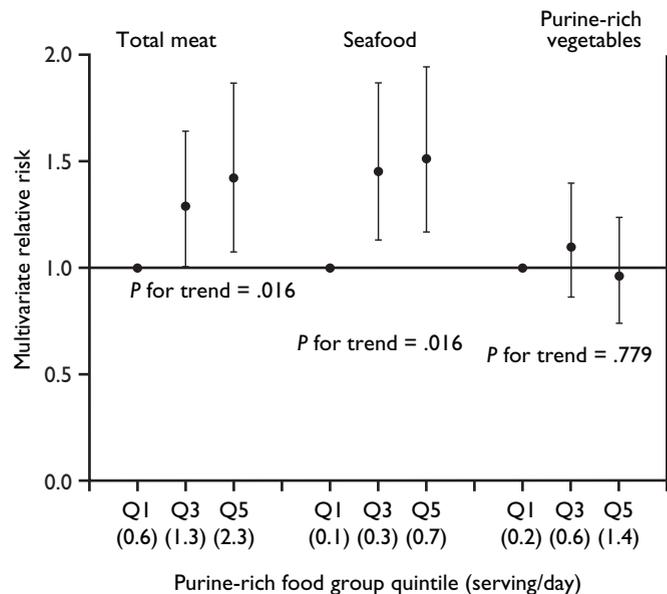
and 1998.¹⁶ The adjusted risk of gout was approximately 40% to 50% greater in those with a diet highest in red meat or seafood compared with those with the diet lowest in these foods (Figure 1). Despite popular belief, the risk of gout was not correlated with consumption of purine-rich vegetables nor total protein intake. Interestingly, high consumption of low-fat dairy products was associated with decreased gout risk, possibly because casein and other milk proteins have uricosuric properties. However, it is thought that reducing dietary purines in patients with gout leads to only modest reductions in serum uric acid levels.⁶⁴ Alcohol consumption increases gout risk in dose-dependent fashion. Beer increases the risk more than liquor (possibly because beer has a higher purine content), whereas wine does not increase risk (Figure 2).¹⁷ Similar associations between hyperuricemia and diet were found in the Third National Health and Nutritional Examination Survey (NHANES).^{65,66}

Problems With Gout Treatment

Pharmacologic treatment of hyperuricemia with urate-lowering drugs has led to a dramatic reduction in long-term gouty arthritis and tophaceous gout.⁶⁷ However, gout is often mismanaged by both physicians and patients alike. Fewer than 10% of patients with gout are referred to rheumatologists, who may have more experience with managing this disease than primary care physicians.⁶⁸ Adherence to gout medications, such as allopurinol, is spotty at best, possibly because patients are not adequately taught how to take them. (For example, allopurinol should not be taken intermittently.)⁶⁹

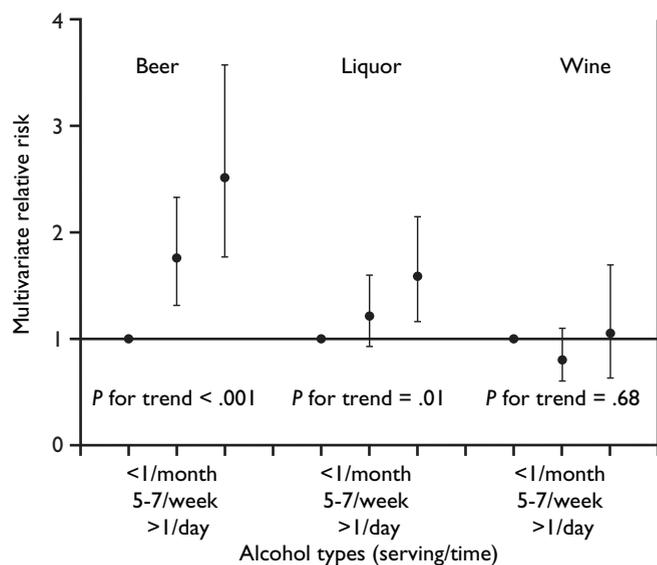
In up to 50% of patients, allopurinol is prescribed for asymptomatic hyperuricemia instead of an approved indication (eg, frequent and debilitating gout attacks, tophi, chronic erosive arthritis, urate nephrolithiasis). The drug should be used cautiously and in reduced dosages in patients with impaired renal function.⁷⁰ More than 50% of cases of allopurinol hypersensitivity syndrome (eg, rash, fever, eosinophilia, hepatitis, renal failure) had been inappropriately treated for asymptomatic hyperuricemia in one study.⁷¹

Figure 1. Associations of purine-rich food groups with gout, from the Health Professionals Follow-up Study (HPFS)



Adapted from Reference 16.

Figure 2. Associations of alcoholic beverages with gout, from the Health Professionals Follow-up Study (HPFS)



Adapted from Reference 17.

Medication errors are often observed in the setting of associated comorbid illnesses and polypharmacy.⁷² Hospitalized patients

with acute gout are often treated with colchicine or nonsteroidal anti-inflammatory drugs, even in the setting of renal failure, which greatly increases the toxicity of these drugs.⁷³ Quality-control indicators have recently been developed, which pertain to the use of urate-lowering medications and anti-inflammatory drugs in patients with gout.⁷⁴

Conclusion

The apparent rise in the prevalence and incidence of gout over the past several decades may be caused by growing populations with risk factors for this disease, such as advanced age, high intake of purine-rich animal protein, metabolic syndrome, diuretic use, organ transplant, and end-stage renal disease. Polyarticular gout can mimic osteoarthritis (especially in elderly women) or rheumatoid arthritis. Hyperuricemia may be an independent cardiovascular risk factor, but treating asymptomatic hyperuricemia cannot be recommended until clinical trials demonstrate that lowering serum uric acid reduces cardiovascular risk. Physicians and patients should be taught how to manage gout properly to minimize the adverse effects of medications.

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