Review
Epidemiology, risk factors, and lifestyle modifications for gout

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Abstract

Gout affects more than 1% of adults in the USA, and it is the most common form of inflammatory arthritis among men. Accumulating data support an increase in the prevalence of gout that is potentially attributable to recent shifts in diet and lifestyle, improved medical care, and increased longevity. There are both nonmodifiable and modifiable risk factors for hyperuricemia and gout. Nonmodifiable risk factors include age and sex. Gout prevalence increases in direct association with age; the increased longevity of populations in industrialized nations may contribute to a higher prevalence of gout through the disorder's association with aging-related diseases such as metabolic syndrome and hypertension, and treatments for these diseases such as thiazide diuretics for hypertension. Although gout is considered to be primarily a male disease, there is a more equal sex distribution among elderly patients. Modifiable risk factors for gout include obesity, the use of certain medications, high purine intake, and consumption of purine-rich alcoholic beverages. The increasing prevalence of gout worldwide indicates that there is an urgent need for improved efforts to identify patients with hyperuricemia early in the disease process, before the clinical manifestations of gout become apparent.

Introduction

Assessing the incidence and prevalence of gout is challenging because of its episodic nature. In the USA gout estimates vary, depending on the population being described. For example, male veterans are at heightened risk for developing gout because of their numerous risk factors, as seen in the Normative Aging Study conducted by the US Department of Veterans Affairs (Fig. 1) [1]. In contrast, white male physicians exhibited a cumulative incidence of gout over a 30-year period of approximately 8.6%, with 5.9% having primary gout (gout without a history of diuretic use) [2]. African-American physicians may have an even higher rate of gout [3]. Although data on physicians cannot accurately be generalized to the public, doctors do more accurately self-report suspected gout than the lay population, from whom many of the other gout estimates were derived.
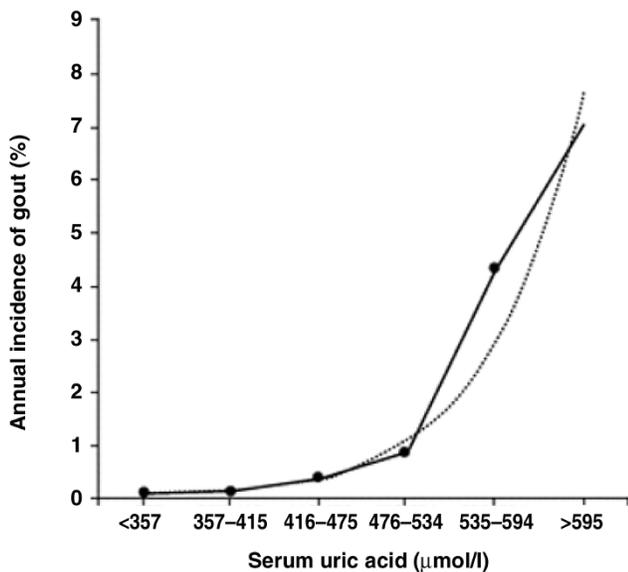
The Rochester epidemiology study [4] has reported on the change in gout incidence over time. Comparing men and women from two cohorts – one from 1977 to 1978 and another from 1995 to 1996 – Arromdee and coworkers found that the age- and sex-adjusted annual incidence rate for primary gout in the USA rose from 20.2/100,000 persons to 45.9/100,000 persons; no change in the incidence of secondary gout related to thiazide diuretic therapy was observed. Gout has also been shown to increase somewhat linearly over a person's lifespan. This perceived rise in gout prevalence is primarily associated with an aging population, but it is also potentially associated with a number of changing societal trends. Based on self-reported gout from the National Health Interview Survey [5], in 1992 about 2 million people were characterized as having gout. In 1996 there were increases in gout incidence of up to 4.6% in men and 2% in women among those in the higher risk age range of 65 years or older, leading to an estimated overall prevalence of between 0.5% and 1%.

The prevalence of gout also appears to be rising in certain populations. A multicenter study conducted in the UK in 1991 found that the prevalence of gout had increased threefold compared with estimates from the 1970s [6]. In a 1999 examination of gout epidemiology from the UK General Practice Research Database [7], gout prevalence was found to be approximately 2% among men and about 1% among men and women combined. Prevalence was highest among those aged 75–84 years; among the men gout incidence approached 8%. Gout prevalence varies substantially by geographic region. In New Zealand among the Maoris gout is relatively endemic with prevalence estimated as high as 5% [8,9]. The prevalence of gout in particular geographic regions suggests that both genetic factors and environmental factors predispose individuals to developing gout [10].

BMI = body mass index; CVD, cardiovascular disease; HDL = high-density lipoprotein.

Figure 1

Cumulative incidence of gouty arthritis by prior urate levels. Reproduced from [1]. Copyright 1987 with permission from Excerpta Medica Inc.

The varied methods of reporting epidemiological data on gout and the sometimes imperfect data sources available make it difficult to document the public health impact accurately. In the Sudbury study [11], for example, in as many as half of the patients who claimed to have gout, this could not be confirmed by history and physical examination. Although it is best to rely on a crystal diagnosis to confirm cases of gout, this is not practical at the population level.

Why is the prevalence of gout potentially rising? One reason may be changes in gout risk factors, not the least of which is increased longevity. As Americans get older and heavier, there has been a concordant rise in the prevalence of hypertension [12,13]. Both the metabolic syndrome and hypertension have a strong association with gout [14,15] (see below), and treatments for hypertension (e.g. thiazide diuretics) can result in the development of secondary gout [16]. Results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial [17] have led to the recommendation that diuretics be given as first-line therapy in most patients with hypertension; some therefore speculate that the incidence of secondary gout related to diuretic use is likely to grow in the near future. The ubiquitous use of low-dose aspirin for the prevention of cardiovascular disease may be another reason for the rise in gout prevalence [18,19].

Nonmodifiable risk factors for gout
Age
The prevalence of gout increases in direct association with age; therefore, the increased longevity of populations in industrialized nations may contribute to a higher prevalence of gout through the disorder's association with age-related diseases (e.g. metabolic syndrome and hypertension) and treatments for aging-related diseases (e.g. thiazide diuretics) [14-16]. Moreover, the prevalence of the clinical manifestations of gout increases with the duration of hyperuricemia. Thus, elderly patients with longstanding hyperuricemia are more likely to present with the signs and symptoms of gout. In one study conducted by Wallace and coworkers [20], individuals older than 75 years exhibited an increase in the rate of gout from 21/1000 persons in 1990 to 41/1000 persons in 1999, and in the 65–74 year age group the increase was from 21/1000 to 24/1000 persons from 1990 to 1992 to more than 31/1000 from 1997 to 1999. In contrast, prevalence rates in persons younger than 65 years remained consistently low throughout the study. In those older than 75 years, the prevalence per 1000 is quite sizable compared with that in younger age ranges; these findings are similar to some of the data from the General Practice Research Database (discussed below).

Sex
Clinically, gout is often considered a male disease. Although gout prevalence has increased in both sexes, among patients younger than 65 years men have a fourfold greater prevalence than women [20]. However, gout in the elderly has a more equal sex distribution, most likely reflecting the loss of the uricosuric effect of estrogen following the menopause. In patients older than 65 years, the sex gap narrows to one woman to every three men with gout and/or hyperuricemia (3:1 ratio). With the declining use of estrogen therapy, the percentage of elderly female patients with gout may increase.

Modifiable gout risk factors
Serum urate
Serum urate level is the most important risk factor for gout. In the Normative Aging Study [1], 2046 initially healthy participants were followed for 14.9 years. Those with baseline serum urate levels of ≥9 mg/dl had a 22% cumulative incidence of gout over a 6-year period. Among patients with urate levels of ≤7.0 mg/dl and 7.0–8.9 mg/dl, the annual incidences of gouty arthritis were 0.5% and 0.1%, respectively (Fig. 1). Large percentages of people in the USA [21] and Japan [22], men in particular, have urate levels above the solubility threshold of approximately 6.7 mg/dl. In patients with gout who are older than 60 years, however, about half are women and the prevalence in women increases as they age.

Medications
Gout is associated with a number of different medications, including diuretics (noted above), low-dose aspirin, and drugs that are commonly used in organ transplantation.

Currently, approximately 46% of women and 59% of men who are at high risk for cardiovascular events take aspirin. Many persons at low risk for cardiovascular events also take

low-dose aspirin in response to the positive publicity surrounding the prevention trials and guidelines [18]. Aspirin has been shown to have a bimodal effect on renal handling of uric acid. At high dosages (>3 g/day) aspirin is uricosuric, whereas at low dosages (1–2 g/day) it causes uric acid retention [23]. At 75 mg/day aspirin resulted in a 15% decrease in the rate of uric acid excretion ($P = 0.045$) and a small but significant increase in serum levels of uric acid ($P = 0.009$) [19]. These effects declined with increasing dosages of aspirin. Concomitant use of diuretics exacerbated the effects of aspirin on uric acid levels.

Renal and other major organ transplants

Hyperuricemia and gout are common complications of renal and other major solid-organ transplants. Gouty joint damage is accelerated in transplant patients with hyperuricemia compared with patients with primary hyperuricemia, and gout is frequently polyarticular [24]. Of transplant patients 13% will experience new-onset gout, and as many as 50% will become hyperuricemic [25]. Among patients receiving heart transplants rates of hyperuricemia are as high as 81%, with 8–12% experiencing new-onset gout [24].

Kidney transplant recipients may develop increased levels of uric acid because its secretion diminishes with the decreasing glomerular filtration rate [26]. Pharmaceutical agents that are commonly prescribed to transplant recipients – including diuretics, antimicrobials such as ketoconazole, ethambutol and pentamidine, and certain immunosuppressive agents such as cyclosporine – are strongly associated with hyperuricemia and gout [27].

Cyclosporine, a calcineurin inhibitor, is thought to increase uric acid levels by reducing tubular uric acid secretion and inhibiting glomerular filtration rates because of its ability to increase renal arterial vasoconstriction [28,29]. A study conducted by Lin and coworkers [30] examined the frequency of hyperuricemia and gout in renal transplant patients who were treated with either cyclosporine and prednisone or azathioprine and prednisone. Hyperuricemia was significantly more common among patients who received cyclosporine than among those who received azathioprine (84% versus 30%; $P = 0.0001$), as was gout (7% versus 0%). Progression from acute gout to chronic, tophaceous gout can occur in as fewer as 6 months in some transplant patients.

The immunosuppressive agent tacrolimus has the potential to increase uric acid through its effect on glomerular filtration rate [31]. However, studies suggest that hyperuricemia occurs in under 3% of patients who receive tacrolimus, and so transplant recipients who receive this agent may be at lower risk for gout than those who receive cyclosporine.

Diet and alcohol intake

The association of purine-rich foods (e.g. meat, seafood, purine-rich vegetables such as peas, beans, and lentils), high

protein intake, and dairy intake was examined in a study conducted by Choi and coworkers [32] in 47,120 men who had no history of gout at baseline. During 12 years of follow up, 730 confirmed new cases of gout were documented. Diet was assessed using the Willett Food Frequency Questionnaire, an instrument that is the 'gold standard' in nutritional epidemiology. Increased meat and seafood intake were associated with 1.41-fold and 1.51-fold increases in risk for gout, respectively, for the highest versus the lowest quintiles of intake. No increase in risk for gout was associated with the intake of purine-rich vegetables or total protein intake. The risk for gout was reduced by nearly 50% in persons in the highest quintile of dairy intake compared with those in the lowest quintile. The majority of these associations were independent of body mass index (BMI), older age, hypertension, alcohol use, diuretic use, and chronic renal failure. Although it was not surprising that meat and seafood had significant associations with the incidence of gout, the lack of effect of purine-rich vegetables in predisposing to gout was a more novel finding. It was also notable that there was a 50% reduction in gout incidence among those consuming the most dairy products (particularly low-fat dairy products).

Alcohol consumption, particularly consumption of purine-rich alcoholic beverages such as beer, is also correlated with an increase in the risk for hyperuricemia. In a second report by Choi and coworkers [33], and including the same cohort as in the previously cited report, a dose–response relationship of alcohol consumption to gout risk was found, after adjusting for other potential confounders. Beer consumption and, to a lesser extent, liquor consumption was shown to increase a person's risk for gout. It should be noted that beer is rich in guanosine, and this was thought to provide a biologic basis for this association. Of note, wine was not a significant risk factor for gout. Although the investigators did an excellent job of accounting for potential confounders, there are clear differences between people who consume wine and those who consume beer and mixed drinks, and the possibility for unmeasured confounding persists. However, adding to the strength of these findings, a subsequent investigation by Choi and Curhan [34] evaluated the relationship between intakes of beer, liquor, and wine and serum uric acid levels using data from 14,809 participants in the Third National Health and Nutrition Examination Survey (NHANES). Both before and after adjustment for other risk factors for hyperuricemia, beer and liquor intake was positively associated with increased serum urate levels (P for trend < 0.001). In contrast, wine intake was significantly associated with reduced serum urate before, but not after, adjustment for other risk factors.

Obesity

Obesity is a growing epidemic in the USA. Presently, approximately 60% of Americans are overweight, and childhood obesity is increasing at an alarming rate [35]. BMI

is significantly associated with risk for gout: compared with persons with a BMI of 21–22.9 kg/m^2, the age-adjusted relative risk for gout is 1.40 for a BMI of 23–24.9 kg/m^2, 2.35 for a BMI of 25–29.9 kg/m^2, 3.26 for a BMI of 30–34.9 kg/m^2, and 4.41 for a BMI of 35 kg/m^2 or higher [15]. Weight gain over time is also associated with risk for gout, even after adjusting for initial weight and other risk factors.

Data suggest that obesity increases serum urate by eliciting both increased production and decreased renal excretion of urate [36]. In the Normative Aging Study [37], weight gain between the first and third visits was positively associated with increases in serum urate. In contrast, weight reduction has been shown in prospective studies to be associated with declines in uric acid levels [38].

Gout and chronic disease associations
A number of diseases have a strong association with gout. This raises the question of cause and effect – do these conditions result from gout, or do these diseases predispose individuals to gout?

The metabolic syndrome
The recent increase in the prevalence and clinical complexity of gout may partly be attributable to hyperuricemia associated with the metabolic syndrome, a clinical entity that is mediated primarily by insulin resistance. The majority of obese patients meet the criteria for metabolic syndrome, which is characterized by a clustering of central obesity; dyslipidemia (hypertriglyceridemia and low high-density lipoprotein [HDL] cholesterol); hypertension (≥130/85 mmHg); insulin resistance, glucose intolerance, or type 2 diabetes mellitus; hyperuricemia; and a prothrombotic and proinflammatory state [39]. In an analysis of data from 8814 men and women aged 20 years or older, the age-adjusted prevalence of the metabolic syndrome was 23.7% from 1988 to 1994 [40]. The prevalence of the metabolic syndrome also varied by ethnicity; for example, among Mexican Americans the age-adjusted prevalence of the metabolic syndrome is 31.9% [41]. Given that the incidence of obesity is rapidly increasing, it is likely that the prevalence of the metabolic syndrome has grown substantially in the intervening decade since these data were recorded.

Components of the metabolic syndrome have been associated with hyperuricemia. In a cross-sectional study conducted in 4053 African-American and Caucasian adults [14], BMI, fasting insulin, and triglycerides were significantly higher, and HDL-cholesterol was significantly lower in male and female individuals with hyperuricemia. BMI had the strongest correlation with urate among the metabolic syndrome components. Insulin resistance was also associated with serum urate levels. However, the influence of fasting insulin was not as strong as that of obesity. After controlling for obesity, insulin, and the other components of the metabolic syndrome, male persons with high triglycerides were more likely to have hyperuricemia. These data suggest that the relationship between hyperuricemia and the metabolic syndrome may result predominantly from the co-variation of these conditions with adiposity and secondarily with insulin level, and – at least in men – elevated triglycerides.
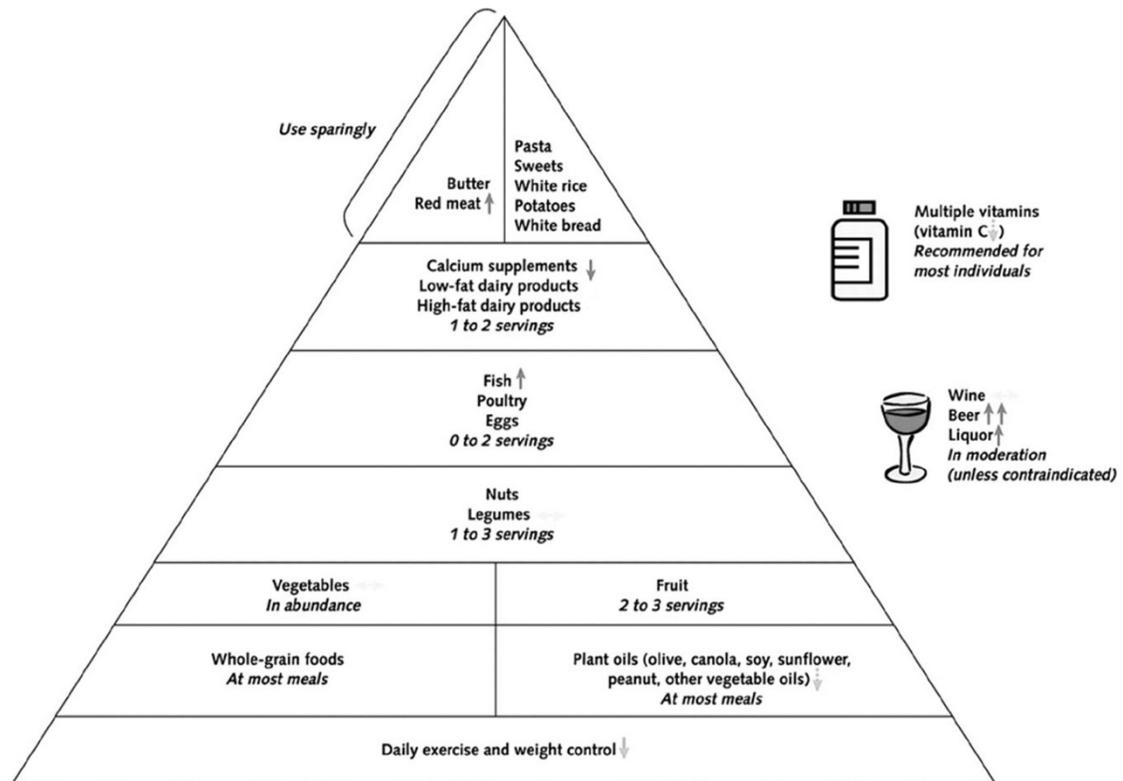
Hypertension
The relationship between hyperuricemia and hypertension is notable, because a higher serum urate level is known to be associated with hypertension. As many as 50% of untreated hypertensive persons have hyperuricemia, which often precedes hypertension, and even among children hyperuricemia has been shown to correlate with blood pressure. In the Normative Aging Study [1], gout was found to be more common among hypertensive individuals, with a strong association with thiazide diuretic use. One issue is whether thiazide diuretics confound the drug effect with hypertension. Sanchez-Lozada and coworkers [42], in their examination of the afferent arterioles in a rat model of gout, found that high urate levels may induce vascular effects that can be attenuated with the use of allopurinol, suggesting grounds for biologic plausibility for this observational association.

Cardiovascular disease
Irrespective of the outcomes of cardiovascular disease (CVD) such as coronary heart disease, ischemic heart disease, new cardiovascular events, or even cardiovascular mortality, CVD is strongly associated with gout. Two large US cohorts that have been rich resources for epidemiologic investigation are the Framingham study and NHANES, which have reached somewhat different conclusions on the associations between cardiovascular events and gout.

Using Framingham data, Culleton and coworkers [43] showed that serum urate levels were not independently associated with CVD, after adjustment for other risk factors. That study suggested that diuretic use, more than gout, was associated with CVD. According to NHANES data [44], the risk for death due to ischemic heart disease increased 1.77-fold in men and 3-fold in women when comparing the highest quartile with the lowest quartile for serum urate. For each 59.5 µmol/l increase in uric acid level, cardiovascular and ischemic heart disease mortality increased. After stratification by cardiovascular risk status, diuretic use, and menopausal status, the relationship between serum urate levels and cardiovascular mortality remained significant except among men using diuretics and men with more than one cardiovascular risk factor. It has been argued that NHANES is a more generalizable cohort than Framingham because it represents a wider spectrum of the US population. However, the Framingham study showed that serum urate may be a confounder for both hypertension and diuretic use, which has called the NHANES data into question.

Recent clinical trial data add fuel to this controversy. In the Losartan Intervention For Endpoint reduction in hypertension

Figure 2

Dietary influences on the risk for gout and their implications within a Healthy Eating Pyramid. Data on the relationship between diet and the risk for gout are primarily derived from the recent Health Professionals Follow-Up Study [15,32,33]. Upward solid arrows denote an increased risk for gout, downward solid arrows denote a decreased risk, and horizontal arrows denote no influence on risk. Broken arrows denote potential effect but without prospective evidence for the outcome of gout. Adapted from [48]. Copyright 2005 with permission from American College of Physicians.

(LIFE) study [45], baseline serum uric acid levels were associated with a 1.02-fold increase in the risk for cardiovascular events per 10 μmol/l increase; this association was significant in women but not in men.

Lifestyle modifications for gout

The data presented above reveal a clear relationship between diet and lifestyle and the development of hyperuricemia and gout. As metabolic disorders, hyperuricemia and gout are often amenable to changes in diet, lifestyle, and medication. As more data on the modifiable risk factors and co-morbidities of gout become available, integration of these data into gout management strategies may become essential, similar to the current management strategies for hypertension [46] and type 2 diabetes [47]. These lifestyle modifications are inexpensive and safe and, when combined with drug therapy, may result in better control of this disorder.

The lifestyle modification recommendations for the treatment or prevention of gout are similar to those for the prevention or treatment of other major chronic disorders [48,49] (Fig. 2). Thus, the net health benefits from these general lifestyle

recommendations [49] are expected to be even greater among patients with gout, particularly those with coexisting insulin resistance syndrome, diabetes, obesity, and hypertension [48]. In particular, weight control, reduced consumption of red meat, and daily exercise are important lifestyle modifications for patients with gout or hyperuricemia and parallel recommendations for the prevention of coronary heart disease, diabetes, and certain types of cancer. Available open-label, interventional data suggest that weight reduction is associated with a decline in uric acid levels [36,38]. Furthermore, data on the relationship between purine-rich foods and urate levels indicate that restricting purine intake can reduce serum uric acid levels. For example, substitution of a purine-free formula diet over a period of days was shown to reduce the blood uric acid of healthy men from an average of 5.0 mg/dl to 3.0 mg/dl [50,51]. In general, dietary restriction of purine-rich foods lowers urinary excretion of uric acid by about 200–400 mg/day and decreases mean serum urate levels by about 1–2 mg/dl [52]. Thus, reducing intake of purine-rich foods, particularly those of animal origin such as red meat, is recommended in the prevention and management of hyperuricemia and gout. Red meat is also the main

source of saturated fats, which are positively associated with insulin resistance [53,54], which in turn is closely associated with gout. These fats also increase low-density lipoprotein cholesterol more than HDL-cholesterol, resulting in an overall negative health effect. Increased consumption of red meat and saturated fats has been linked to major disorders such as coronary artery disease, type 2 diabetes, and certain types of cancer. Thus, it is important for patients with gout to limit red meat consumption, as is indicated by the new Healthy Eating Pyramid recommendations for the general public (Fig. 2) [49].

For cardiovascular benefit, instead of consuming fish, patients with gout could consider taking plant-derived ω3 fatty acids or eicosapentanoic acid and docosahexanoic acid supplements. Experimental evidence also suggests that diets enriched with γ-linolenic acid and eicosapentaenoic acid significantly reduce urate crystal induced inflammation; however, the effect of such a diet on the clinical course of gout has not yet been studied [55].

The recent recommendations on dairy consumption for the general public may be applicable in most patients with gout or hyperuricemia, and may offer additional benefit to those individuals with hypertension, diabetes, and cardiovascular disorders [32,56]. Further risk–benefit assessments in specific clinical contexts would be helpful. Daily consumption of nuts and legumes, as recommended by the Harvard Healthy Eating Pyramid [49], may also provide important health benefits without increasing the risk for gout [32]. New data on the incidence of gout suggest that a daily glass of wine might provide health benefits without raising the risk for gout, as opposed to beer or liquor consumption [33,57]. However, reducing or eliminating alcohol – particularly purine-rich beverages such as beer and certain liquors – is generally recommended due to the significant effect on uric acid levels.

Several studies have suggested that high doses of vitamin C have a uricosuric effect [58-62]. For example, one study [61] showed that ingestion of 4.0 g ascorbic acid led to a twofold increase in fractional clearance of uric acid up to 6 hours after ingestion, and that ingestion of 8.0 g ascorbic acid for 3–7 days reduced serum uric acid by up to 3.1 mg/dl as a result of sustained uricosuria. A recent trial indicated that taking 500 mg/day vitamin C for 2 months reduced serum uric acid by 0.5 mg/dl [62]. Because vitamin C is generally considered safe, its uricosuric effect may provide a potentially useful option for the prevention and management of hyperuricemia and gout.

Conclusion
Emerging data on the epidemiology of gout suggest that the prevalence of gout is rising. Advancing age increases the prevalence of gout; this is partly attributable to the increased risk factors for gout – including metabolic syndrome, hypertension, and renal disease – that are associated with age. New data is emerging on risk factors for gout, and of note is

the increasingly strong association of hyperuricemia with both hypertension and CVD.

The increasing prevalence of gout worldwide indicates that there is an urgent need for improved efforts to identify patients with hyperuricemia early in the disease process and before the clinical manifestations of gout become apparent. Lifestyle modifications, including weight loss, dietary changes, hypertension control, and changes in medication regimens, may provide adequate control of hyperuricemia in some patients, particularly when they are instituted early in the course of disease; they may also result in better control of gout in other patients when combined with drug therapy.

Competing interests

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