Diet, Alcohol, and Gout: How Do We Advise Patients Given Recent Developments?

Hyon K. Choi, MD, DrPH

Address
Rheumatology Unit, Bulfinch 165, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA.
E-mail: hchoi@partners.org

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The disease burden of gout remains substantial and may be increasing as a result of trends in demographics and lifestyles. Recent scientific data serve to illuminate the links between dietary and other factors and risk for gout. These lifestyle factors affect not only the risk for gout, but also are risk factors for other chronic diseases of public health importance. Accordingly, dietary and lifestyle recommendations related to gout should consider their effect on many diseases beyond gout. These recommendations should reinforce established recommendations where the influence on gout parallels the influence on other diseases, and consider modifying the recommendations where they are divergent.

Introduction

Epidemiologic studies suggest that the overall disease burden of gout remains substantial and may be increasing. The prevalence of self-reported physician-diagnosed gout in the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994) was found to be greater than 2% in men over 30 years of age and in women over 50 years of age [1•]. The prevalence increased with increasing age and reached 9% in men and 6% in women over 80 years of age [1•]. These may be overestimates given that they were based on self-reports of physician-diagnosed gout; however, even if the true age-specific prevalences were 50% lower [2], they would still be substantial. Furthermore, the incidence of primary gout (*ie*, without diuretic exposure) doubled over the past 20 years according to the Rochester Epidemiology project, whereas the proportion of gout associated with diuretic use decreased significantly during the period [3•]. The Mayo study documenting increasing incidence of gout found only slight changes in nondietary risk factors (*eg*, increase in body mass index and the proportion of hypertension and decrease in the proportion of alcoholism). These changes were not statistically significant, thus not explaining the increased incidence [3•]. Notably, the study did not investigate dietary factors and concluded that there may be unidentified risk factors contributing to the increasing incidence [3•]. It is conceivable that the dietary change over the past few decades may explain part of the increasing incidence for gout.

In a recent study, the relation between these purported dietary risk factors and incident gout was prospectively examined over a 12-year period in 47,150 male participants (the Health Professionals Follow-up Study [HPFS], 730 incident gout cases) with no history of gout at baseline [4••,5••]. The study confirmed some of the long-standing suspicions (red meat, seafood, beer, and liquor), exonerated others (protein, wine, and purine-rich vegetables), and also identified potentially new protective factors (dairy products). There are also other, potential dietary factors that are shown to significantly influence the urate levels, thus possessing the potential to affect the risk for gout. Dietary or lifestyle recommendations based on these findings should take into account other associated health benefits and risks, since many of these factors have health effects beyond their influence on gout. This consideration of other health effects appears particularly important among patients with gout, since the disease often coexists with a number of important chronic disorders such as the insulin resistance syndrome, obesity, and hypertension [6,7,8••]. This paper reviews the recent advances in this area in detail and attempts to put these findings into the context of clinical and public health decision making in the prevention and management of gout. Other potential health implications of these findings are reviewed using the recent dietary recommendation for the general public—Healthy Eating Pyramid (Fig. 1) [9••].

Meat Intake

The HPFS showed that men in the highest quintile of meat intake had a 41% higher risk for gout compared with the lowest quintile [4••]. Correspondingly, in a nationally representative sample of US men and women, higher levels

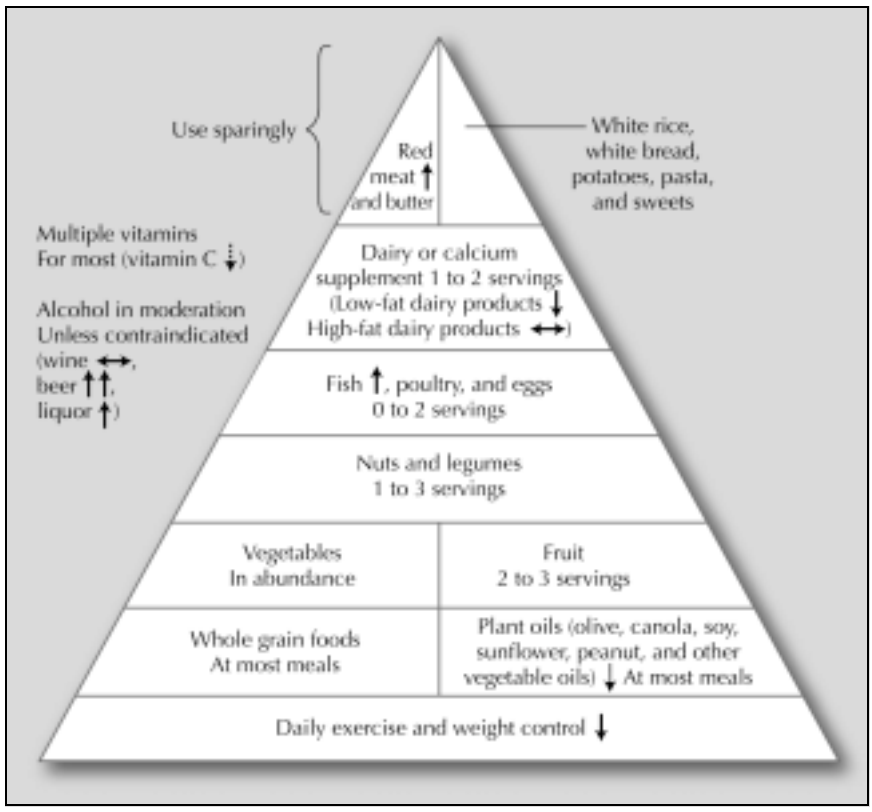

Figure 1. Dietary impacts on the risk for gout and their implications within the new healthy eating guideline pyramid. Data on the relation between diets and the risk for gout are primarily based on the recent large prospective study (Health Professionals Follow-up Study) [4••,5••,8••]. Upward solid arrows denote an increased risk for gout, whereas downward solid arrows denote a decreased risk. Horizontal arrows denote no influence on the risk for gout. Dotted arrows denote potential effect, but yet without prospective evidence for the outcome of gout. (*Adapted from* Willett and Stampfer [9••].)

of meat were associated with higher serum uric acid levels [10•]. Specifically, more than two weekly servings of beef, pork, or lamb as a main dish was associated with a 50% increased risk for gout as compared with less than one serving per month (*P* for trend = 0.01) [4••]. The mechanism behind this increased risk may be multifactorial. The urate-raising effect of artificial short-term loading of purified purine has been well-demonstrated by metabolic experiments in animals and humans [11–14]. Further, red meat is the main source of saturated fats, which are positively associated with insulin resistance [15,16], which reduce renal excretion of urate [17–20]. These fats also increase low-density lipoprotein cholesterol levels more than high-density lipoprotein (HDL) cholesterol creating a negative net effect. Higher levels of these fat or red meat consumption has been linked to major disorders such as coronary artery disease, type 2 diabetes, and certain types of cancer. Thus, it would be important for patients with gout to limit red meat consumption as it also sits at the top of the recent Healthy Eating Pyramid for the general public (Fig. 1) [9••].

Seafood and Omega-3 Fatty Acids

The HPFS found that men in the highest quintile of seafood intake had a 51% higher risk for gout compared with the lowest quintile [4••]. Increased intake of tuna, dark fish, other fish; and shrimp, lobster, or scallops was all associated with an increased risk for gout (*P* for trend < 0.05 for all items). Correspondingly, in a nationally representative sample of US men and women, higher levels of seafood consumption were associated with higher serum uric acid levels [10•].

The recommendation about seafood in prevention of gout appears more complicated than that for meat intake because oily fish and omega-3 fatty acids reduce the incidence of cardiovascular disorders according to many studies including epidemiologic studies and clinical trials [21]. Based on these data, the American Heart Association (www.americanheart.org) concludes that omega-3 fatty acids benefit the hearts of healthy people and those at high risk for (or who have) cardiovascular disease and currently recommends eating fish (particularly oily fish) at least twice weekly [21]. Prospective secondary prevention studies suggest that eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) supplementation ranging from 0.5 to 1.8 g/d (as fatty fish or supplements) significantly reduces subsequent cardiac and all-cause mortality [21]. Similarly, total intakes of 1.5 to 3 g/d of α-linolenic acid seem beneficial [21]. Cardiovascular prevention may be more relevant among gouty patients, since the associated comorbidities of gout (*eg*, insulin resistance syndrome, hypertension) or gout itself may pose an increased risk for cardiovascular disease [22]. Thus, among patients with gout or hyperuricemia, the use of plant-derived omega-3 fatty acids or supplements of EPA and DHA could be considered in the place of fish consumption. This approach would provide the benefit of omega-3 fatty acids likely avoiding the increased risk for gout from the purine load contained in seafood. Further, diets enriched in

linolenic acid and EPA significantly suppress urate crystal induced inflammation in a rat model [23,24] raising an intriguing potential protective role of these fatty acids against gout flare.

Dairy Intake

According to the HPFS study, men in the highest quintile of dairy intake had a 44% lower risk for gout compared with the lowest and the inverse association was limited to low-fat dairy consumption [4••]. Men in the highest quintile of dairy protein intake had a 48% lower risk for gout compared with the lowest quintile [4••]. Correspondingly, in a nationally representative sample of US men and women, dairy consumption was inversely associated with the uric acid level [10•]. Dairy protein may exert its urate-lowering effect without the concomitant purine load contained in other animal protein sources such as meat and seafood, given that dairy products have a low purine content [25,26]. The absence of the inverse association with high-fat dairy products could result from the counteracting effect of saturated fats contained in high-fat dairy products. Studies have suggested that low-fat dairy foods are associated with several potential health benefits including a lower incidence for coronary heart disease [27], premenopausal breast cancer [28], colon cancer [29], and type-2 diabetes [30]. Further, low-fat dairy foods have been one of the main components of dietary approaches to stop hypertension diet that has been shown to substantially lower blood pressure [31]. However, dairy consumption including low-fat dairy foods has been implicated in possible increases in prostate cancer [32]. Weighing these benefits and risks, the recent dietary guideline for the general public recommends one to two daily servings of dairy products (Fig. 1) [9••]. This recommendation would be generally applicable among patients with gout or hyperuricemia, perhaps with added benefits for their comorbidities such as hypertension, diabetes, and cardiovascular disorders. Further confirmation of these findings and risk-benefit assessments in each specific clinical context are also expected to be helpful in making recommendations for dairy consumption.

Purine-rich Vegetables

The consumption of purine-rich vegetables was not associated with the risk for gout [4••]. Similarly, intake of individual purine-rich vegetable items was not associated with the risk for gout including nuts, legumes, spinach, mushrooms, oatmeal, and cauliflower. Men in the highest quintile of vegetable protein actually had a 27% lower risk for gout compared with the lowest quintile. These findings may have important implications among gouty patients, since these vegetables (especially, nuts and legumes) are excellent sources of protein, fiber, vitamins, and minerals. Studies have suggested that nut consumption is associated with several important health benefits including a lower incidence for coronary heart disease [33,34], sudden cardiac deaths [35], gallstone [36,37], and type-2 diabetes [38]. Many kinds of nuts contain healthy fats, and controlled feeding studies show that nuts improve blood cholesterol ratios [9••]. Legumes or dietary patterns with increased legume consumption have been linked to a lower incidence for coronary heart disease [39–41], stroke [42], certain types of cancer [43,44], and type-2 diabetes [45]. The recent healthy eating pyramid recommends one to three times daily consumption of nuts and legumes (Fig. 1) [9••], which appears readily applicable among patients with gout or hyperuricemia.

Alcoholic Beverages

In the HPFS, increasing alcohol intake was associated with increasing risk for gout (a dose-response relationship) [5••]. Compared with abstinence, daily alcohol consumption 10–14.9 g increased the risk for gout by 32%; 15–29.9 g by 49%; 30–49.9 g by 96%; and greater than 50 g by 153% (P for trend < 0.001). Beer consumption showed the strongest independent association with the risk for gout (multivariate relative risk [RR] per 12-oz serving per day 1.49; 95% confidence interval [CI] 1.32–1.70). Consumption of liquor was also significantly associated with gout (multivariate RR per drink or shot per day 1.15; 95% CI 1.04–1.28); however, wine consumption was not (multivariate RR per 4-oz serving per day 1.04; 95% CI, 0.88–1.22) [5••]. Correspondingly, a US national survey study demonstrated parallel associations between these alcoholic beverages and serum urate levels [46•].

These findings confirmed the long-held belief of relation between alcohol intake and the risk for gout. In addition, they suggest that certain nonalcoholic components that vary among these alcoholic beverages play a major role in the incidence for gout. Beer is the only alcoholic beverage acknowledged to have a large purine content, which is predominantly guanosine, a readily absorbable nucleoside [47,48]. The effect of ingested purine in beer on the blood uric acid may be sufficient to augment the hyperuricemic effect of alcohol itself producing a greater risk for gout than liquor or wine [5••]. There may be other nonalcoholic offending factors, particularly in beer. Wine is known to contain a number of nonalcohol components including antioxidants [49–51], vasorelaxants [52], and stimulants to antiaggregatory mechanisms [53]. Since uric acid is considered as an indicator for increased oxidative stress, nonalcoholic components in wine (*eg*, polyphenols with antioxidant properties [49–51]) may potentially play a role in mitigating the impact of alcohol on serum uric acid.

The health benefits of moderate drinking likely outweigh the risks, especially among those with demographics of the highest prevalence for gout (*eg*, middle aged men). More than 60 prospective studies consistently demon-

strated that moderate alcoholic consumption is associated with a 25% to 40% reduced risk for coronary heart disease [54]. Also, a number of prospective studies also suggest a similar degree of protective effect against ischemic stroke, peripheral vascular disease, sudden cardiac death, and death from all cardiovascular causes [54]. The benefits of moderate drinking appear to go beyond the heart. For example, moderate drinking has been linked to a decreased risk for gallstones [55] and type-2 diabetes [56] as compared with abstinence. Based on these data, the recent Healthy Eating Pyramid for the general public allows moderate alcohol consumption (Fig. 1) [9••], especially if you already drink alcohol. The key is to keep the consumption in the moderate range (*ie*, one to two drinks per day for men, and no more than one drink per day for women [57]). However, starting drinking is not generally recommended, since similar benefits can be achieved with exercise or healthier eating [57].

These other health effects of moderate drinking may be considered in advising about alcohol intake to patients with existing gout or at a high risk for developing gout. For example, if you are a middle-aged man with no history of alcoholism who is at moderate to high risk for heart disease and gout (incident or recurrent), a daily wine drink could bring associated health benefits perhaps without increasing the risk for gout attacks. This approach may be especially beneficial if the patient has low HDL-cholesterol that is not responsive to diet and exercise therapy because moderate amounts of alcohol raise levels of HDL-cholesterol [58]. Meanwhile, the HPFS [5••] and National Health and Nutrition Examination Survey study [46•] suggest that moderate consumption of beer or liquor is associated with gout and uric acid levels, thus providing less favorable risk-benefit ratios than wine among patients with gout or hyperuricemia.

Other Potential Dietary Factors

The only carbohydrate that has been shown to exert a direct effect on uric acid metabolism is fructose [48]. After intravenous fructose, uric acid production is rapidly enhanced, because of accentuated degradation of purine nucleotides [59] or increased purine synthesis [48,60]. Oral fructose may also increase blood uric acid levels, especially in those with hyperuricemia [61] or a history of gout [62].

Fructose consumption in the US has increased substantially over the past decades [63]. The commercial production of high-fructose corn syrup began in 1967, at which time the fructose content of the syrup was 15% [63]. After a few more modifications, high-fructose corn syrup with a fructose content of 55% became the sweetener of choice for the soft drink and ice cream industries, and a high-fructose corn syrup with a fructose content of 90% became a frequent choice for use in "natural" and "light" foods [63]. By 2002, high-fructose corn syrup sweeteners represented 56% of the US nutritive sweetener market. This endemic use of high-fructose corn syrup has been implicated in the increasing frequency of the insulin resistance syndrome, type-2 diabetes, and obesity [63,64]. It is conceivable that increased fructose intake may also have contributed to the increasing incidence for gout.

Several studies suggest that high doses of vitamin C show a uricosuric effect [65–68]. For example, ingestion of 4.0 g of ascorbic acid led to a two-fold increase in fractional clearance of uric acid up to 6 hours after the ingestion and ingestion of 8.0 g of ascorbic acid for 3 to 7 days reduced the serum uric acid by up to 3.1 mg/dL as a result of a sustained uricosuria [68]. The uricosuric effect of ascorbic acid may be because of competition with uric acid for renal tubular anion-exchange reabsorptive transport [66,68]. Since vitamin C is generally considered safe, its uricosuric effect may provide a potentially useful option for the prevention and management of hyperuricemia and gout.

In addition, a recent Taiwanese case-control study (91 gout cases and 91 controls) suggested a protective effect of folate and dietary fiber against gout (odds ratios, 0.43 and 0.37 between the extreme tertiles, respectively) [69•]. These interesting findings call for prospective confirmation.

Adiposity and the Risk for Gout

Adiposity has been positively associated with serum uric acid levels and proposed to increase the risk for gout. Although several prospective cohort studies have evaluated the association between obesity and gout [22,70–72], the lack of data and small number of gout cases limited the comprehensive adjustment of relevant covariates. Specifically, no prospective information had been available about the relation between obesity and incident gout after adjusting for dietary factors, which themselves may be risk factors for gout and vary with adiposity. The recent HPFS found that body mass index and waist-to-hip ratio were strong risk factors for incident gout in men, independent of other risk factors including dietary factors [8••]. Compared with men with body mass index 21–22.9 kg/m^2, the multivariate RRs of gout were 1.95 (1.44 to 2.65) for men with body mass index 25–29.9 kg/m^2, 2.33 (1.62 to 3.36) for 30–34.9 kg/m^2, and 2.97 (1.73 to 5.10) for greater than 35 kg/m^2 (P for trend < 0.001). The multivariate RR for gout among men in the highest waist-to-hip ratio quintile (0.98–1.39) as compared with those in the lowest (0.70–0.88) was 1.82 (95% CI, 1.39–2.39; P for trend, < 0.001). Further, compared with men who maintained their weight (-4 to +4 lbs) since age 21, the multivariate RR of gout for men who gained 30 lb or more was 1.99 (1.49 to 2.66). In contrast, the multivariate RR for men who lost 10 lb or more since the study baseline was 0.61 (95% CI, 0.40–0.92) [8••]. Increased adiposity may lead to hyperuricemia through increased production and decreased renal excretion of urate [24,73]. Factors not related to uric acid such as chronic joint trauma because of

excess weight have been proposed as an additional explanation for the association between obesity and gout [6,24].

The impact of adiposity on gout adds to the already substantial hazards associated with the obesity epidemic in the United States. The 1999–2000 National Health and Nutrition Examination Survey estimated that the age-adjusted prevalence of obesity (body mass index > 30) among US adults is 30.5% [74]. The prevalence of class 3 obesity (body mass index 40) among adults has more than doubled in 10 years, with an estimated prevalence of 2.2% in the year 2000 [75]. Obesity is associated with at least as much morbidity as are poverty, smoking, and problem drinking [76] and leads to approximately 300,000 deaths per year in the United States [77]. For example, weight gain has been linked to increased risks for coronary heart disease [78,79], hypertension [80], type-2 diabetes [56,81], kidney stone [82], and gallstones [83]. The new Healthy Eating Pyramid strongly recommends daily exercise and weight control by placing them as the foundation of the pyramid (Fig. 1) [9••]. Comprehensive persistent effort to reduce adiposity could contribute to reducing the disease burden from gout and associated morbidities [20].

Conclusions

Dietary guidelines for patients with gout should consider other related health benefits and risks, since the disease is often associated with major chronic disorders. It would be important for patients with gout or hyperuricemia to control their weight with daily exercise and to limit red meat consumption, recommendations that are in parallel with those related to coronary heart disease, diabetes, and certain types of cancer. These patients could consider the use of plant-derived omega-3 fatty acids or supplements of EPA and DHA in place for fish consumption for cardiovascular benefits. The recent recommendation on dairy consumption for the general public would also be applicable among patients with gout or hyperuricemia, perhaps with added benefits for their comorbidities such as hypertension, diabetes, and cardiovascular disorders. Further risk-benefit assessments in each specific clinical context would be helpful. Daily consumption of nuts and legumes recommended by the Healthy Eating Pyramid [9••] may also provide important health benefits without increasing the risk for gout. Similarly, a daily wine drink may bring health benefits associated with moderate drinking without imposing an elevated risk for gout, especially in contrast to beer or liquor consumption. Nonetheless, the available literature examining the association between diet and gout are limited, compared with that for more common medical conditions such as cardiovascular disorders. Also, a dietary strategy that is effective for primary prevention may not always translate into an effective secondary prevention strategy among patients with existing disorders. More research is needed to drive robust conclusions that may lead to sound recommendations.

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