HHS Public Access

Author manuscript

Best Pract Res Clin Rheumatol. Author manuscript; available in PMC 2022 December 01.

Published in final edited form as:

Best Pract Res Clin Rheumatol. 2021 December ; 35(4): 101723. doi:10.1016/j.berh.2021.101723.

Role of Diet in Hyperuricemia and Gout

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Abstract

Background: Gout is the most common form of inflammatory arthritis, affecting 41 million adults worldwide. The global burden of gout has been increasing over the last three decades, yet its management remains suboptimal. The primary aim of this manuscript is to review the impact of various diets such as the DASH, Mediterranean, and low purine diets; weight loss; and individual foods including alcohol, caffeine, cherry, dairy, high-fructose corn syrup, omega-3 fatty acids, and vitamin C on hyperuricemia and clinical gout outcomes such as flares and tophi.

Conclusion: Few studies to date have specifically evaluated the effect of various dietary approaches on hyperuricemia among people with gout and on gout-specific outcomes. Overall, the dietary factors appear to have a small effect on serum urate levels and their impact on the long-term clinical course of gout is uncertain. Limited evidence suggests that avoidance of certain foods and beverages may decrease the frequency of gout flares. Weight loss may be beneficial for prevention as well as treatment of gout. Urate lowering therapy remains the mainstay of therapy, with diet and dietary factors studied to date playing a limited role in the definitive management of gout.

Keywords

Gout; Hyperuricemia; Dietary Factors; Diet; Body Mass Index

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Author contributions- All authors have contributed to the following: (1) the conception and design of the article, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval

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Conflicts of Interest Statement: The authors have no conflicts of interest to disclose.

Introduction and Background:

According to the latest Global Burden of Disease (GBD) estimates, gout is the most common cause of inflammatory arthritis, affecting 41 million people worldwide (1). According to the 2015 – 2016 National Health and Nutrition Examination Survey (NHANES) survey, 3.9% (9.2 million) of US adults have gout (2). Unfortunately, despite good understanding of the disease pathophysiology and available therapies, the burden of gout remains high and gout management remains suboptimal (3). The burden of gout is compounded by the additional impact of comorbidities that are prevalent in patients with gout including hypertension (75%), chronic kidney disease (CKD) (70%), obesity (53%) and cardiovascular disease (CVD) (10% to 14%), which are associated with increased morbidity and mortality risk (4). Patients with gout also have a higher incidence of metabolic syndrome (5), and asymptomatic hyperuricemia is more prevalent in individuals with metabolic syndrome (6, 7). Diet plays an integral role in several of these chronic medical conditions that are common in gout, and diet is also hypothesized to play a role in hyperuricemia and gout via the contribution of dietary purines, leading to increased urate production. Given the importance of diet and metabolic factors in many of the common comorbidities in patients with gout and the recognized contributions of certain foods to serum urate, there has been much interest in the potential effects of dietary approaches in gout management.

In this review, we focus on dietary approaches and individual dietary factors that have been studied for their impact on hyperuricemia and gout.

Production and Excretion of Urate:

Adenine and guanine are purine nucleotide bases that are essential for the formation of DNA and RNA in the form of nucleosides (adenosine, guanosine). As triphosphates (e.g., ATP), they help in cellular energy transfer and utilization. They are also components of co-enzymes and play a significant role in neurotransmission (8). Thus, purines are critical factors for normal human physiologic functioning. The link between purines and gout stems from the fact that purine breakdown leads to production of urate, though in the majority of individuals, this process does not lead to hyperuricemia. Several enzymatic reactions lead to the conversion of purines into uric acid (Figure 1). The monophosphates Adenosine Monophosphate (AMP) and Guanosine Monophosphate (GMP) are metabolized by nucleotidases into adenosine and guanosine. Adenosine is metabolized into inosine by adenosine deaminase, which is further metabolized by purine nucleoside phosphorylase (PNP) into hypoxanthine, after which xanthine oxidase metabolizes it into xanthine, and then into urate. Similarly, guanosine, a precursor of guanine, is metabolized by PNP into guanine, and then guanine deaminase metabolizes it into xanthine, after which xanthine oxidase metabolizes it into urate. These steps in purine metabolism are illustrated in Figure 1.

As a final step prior to excretion, in many organisms, urate is broken down by the enzyme uricase to 5 – hydroxyisourate and subsequently allantoin, which is highly water soluble and excreted by the kidney. However, humans and higher primates such as gorillas and

chimpanzees lack uricase. Urate is thus the end-product, which is not water soluble and requires active excretion. These organisms thus have higher circulating levels of urate (9). When urate levels exceed 6.8 mg/dL, crystallization can occur, which ultimately leads to clinical manifestations of gout.

Hyperuricemia results from either urate overproduction or renal and/or gastrointestinal underexcretion or both (10), though underexcretion is the predominant cause of hyperuricemia in people with gout (11) (12). Approximately 1/3 of the body urate pool is derived from diet whereas contributions from endogenous production is ~2/3 (13). The larger issue in gout, though, is urate underexcretion. Approximately two-thirds of the urate is excreted by the kidneys, and the remainder by the gastrointestinal tract.

Dietary factors, hyperuricemia and gout:

Beyond medications, there is much interest in whether dietary approaches can be leveraged as an adjunct to optimize gout management and/or as an option for patients who do not yet meet indications for urate-lowering therapy. The degree to which diet impacts gout management remains controversial. Underexcretion of urate is a major contributor to hyperuricemia in gout, and the majority of urate production is related to metabolism of endogenous purines rather than from exogenous dietary sources (13). Nonetheless, therapeutically, the most common approach to gout management has been in addressing urate production with use of xanthine oxidase inhibitors. Dietary factors would also largely influence urate production, though some may also potentially operate by affecting urate excretion.

We review here diets such as the Dietary Approaches to Stop Hypertension (DASH) diet, Mediterranean diet, and low purine diet; weight loss; and individual foods including alcohol, caffeine, cherry, dairy, high-fructose corn syrup, omega-3 fatty acids, and vitamin C. We specifically comment upon their reported associations with serum urate, risk of developing gout, and clinically relevant outcomes among people with gout when data are available, namely flares and tophi.

Relative Contributions to Hyperuricemia by Genetics and Diet

Several studies have evaluated both genetic and dietary contributions to hyperuricemia. In a meta-analysis of 6 cohort studies that included 16,760 patients, the variance in serum urate in the general population was better explained by genetic contributions compared to urate-modifying dietary factors, namely beer, liquor, wine, soft drinks, skimmed milk and meat (14). Each of these foods contributed ~1% of the variation in serum urate, while genetic polymorphisms were estimated to contribute 23.9% of the variation in serum urate. A study involving 419,060 participants of European ancestry also concluded that diet had a relatively minor role in determining serum urate and hyperuricemia based upon population attributable fractions, while Body Mass Index (BMI) and genetic polymorphisms had much larger contributions (15). On the other hand, an analysis of 44,654 men from the prospective Health Professionals Follow-up Study who were free of gout demonstrated that among overweight and normal weight men, a combination of the DASH diet, no alcohol intake

and no diuretic use could prevent more than 50% of incident gout, but in obese patients, these interventions would not prevent incident gout, suggesting that obesity is an important risk factor for development of gout that outweighs any potential beneficial effects of dietary patterns (16). Another study further illustrated that population attributable fractions may offer different insights than 'variance explained' for exposures that are highly prevalent (17). Authors reported that the adjusted serum urate differences between the highest and lowest deciles and percentiles of the DASH diet were 0.16 mg/dL and 0.44 mg/dL, respectively, highlighting the relatively small impact of diet on serum urate. On the other hand, this study supported the important contributions of obesity on serum urate levels, 44% of hyperuricemia cases attributed to being overweight or obese, with variance in serum urate being 8–9%.

Thus, while diet may contribute to hyperuricemia, genetic contributions and obesity itself appear to be larger drivers of hyperuricemia in the general population. As such, dietary changes may not have a large impact on serum urate among people with gout in whom much larger reductions in serum urate are typically needed for disease control.

Role of specific diets in hyperuricemia and gout:

The three main diets that have been evaluated in relation to hyperuricemia and gout are the Dietary Approaches to Stop Hypertension (DASH) diet, Mediterranean diet, and a low purine diet. We review the data related to each of the 3 types of diets below.

Dietary Approaches to Stop Hypertension (DASH) Diet:

The DASH diet was initially developed for the management of hypertension. It is a plant-focused diet, rich in fruits, vegetables, nuts, with low-fat and non-fat dairy, lean meats, fish, poultry, mostly whole grains, and "heart healthy" fats. It recommends limited quantity of red meats, sweets, sugary beverages, saturated fat, total fat and cholesterol.

Several studies have provided insights regarding the effects of the DASH diet on serum urate in non-gout samples. A secondary analysis of the original DASH RCT among people with hypertension but without gout, who were on a DASH diet, demonstrated a 0.22 mg/dL (95% CI −0.35, −.0.08) reduction in serum urate with the DASH diet (baseline serum urate 5.59 ± 1.55 mg/dL; final 5.37 ± 1.42 mg/dL) as compared to 0.03 mg/dL (95% CI −0.10, 0.16) reduction with typical American diet (baseline serum urate 5.65 ± 1.56 mg/dL, final 5.68 ± 1.55 mg/dL). The difference between both groups was statistically significant, though the reduction in mean serum urate was small (18). A third group was assigned to a diet predominant in fruits and vegetables, which was associated with 0.17 mg/dL reduction (95% CI, −028, 0/16); baseline 5.85 ± 1.27 mg/dL, final 5.68 ± 1.27 mg/dL). There was no significant difference between the DASH and the fruit and vegetable diets.

An analysis of a subset of participants in the DASH-Sodium trial among prehypertensive and hypertensive individuals without gout demonstrated that participants in DASH diet group (mean baseline urate 6.6 mg/dL) achieved 1 mg/dL reduction in urate levels at day 90, compared with 0.1 mg/dL reduction by control group who were on diet isocaloric to the DASH diet, similar to the American Diet (baseline urate 6.7 mg/dL) (19).

A secondary analysis of the Optimal Macronutrient Intake Trial to Prevent Heart Disease feeding study (OmniHeart) conducted among people with prehypertension or hypertension demonstrated minimal effects of a protein-rich DASH diet on serum urate, with a reduction of 0.16mg/dL (mean baseline serum urate ± SD of 5.1 ± 1.2 mg/dL) (20). Of note, these studies were conducted among people without gout, and participants were enrolled regardless of their serum urate (i.e., no exclusions related to hyperuricemia).

One study provides insight into the impact of the DASH diet on urate among people with gout. In this pilot crossover RCT, 43 adults with gout were randomized to receiving dietician-directed groceries (DDG) patterned on the DASH diet versus self-directed groceries (SDG) in the first block and crossed over without a washout. Those who started with the DDG had a decline in their serum urate of 0.55mg/dL, whereas the SDG group had no change. However, in the second half of the study, the results were opposite, with a 0.48 mg/dL reduction in serum urate in the SDG group and 0.05 mg/dL in the DDG group, and overall there was no within-person differences between the two periods (21). This may have been secondary to a carryover effect from lack of a washout period.

In terms of impact of the DASH diet on risk of developing gout, a cohort study conducted in the Health Professional Follow-up Study reported that higher DASH diet scores were associated with lower risk of developing gout (22). In this study, 44,444 men with no history of gout were followed for 26 years. A total of 1731 cases of gout were documented over the follow-up period. Men in the highest quintile compared with those in the lowest quintile of the DASH dietary pattern score had a 32% lower risk (relative risk 0.68 (95% CI 0.57, 0.80)) of developing gout. In contrast, the relative risk of developing gout among men in the highest versus lowest quintile of the Western dietary pattern score was 1.42 (95% CI 1.16, 1.74).

There are no studies published to date evaluating the effects of the DASH diet on gout flares or tophi. Given the modest decrease in serum urate with the DASH diet among people without gout, and minimal data to date in people with gout, it is unclear that a meaningful impact on clinically relevant outcomes in gout would be realized with the DASH diet alone.

The 2020 ACR guideline for the management of gout does not make specific recommendations about the DASH diet due to overall low quality of evidence among people with gout. (23)

The Mediterranean Diet:

The Mediterranean Diet emphasizes intake of plant proteins, whole grains, fish, use of monounsaturated fat (e.g., olive oil), with moderate wine consumption, and low intake of red meat and refined grains (24). The Mediterranean Diet, especially if supplemented with extra virgin olive oil or nuts, has been associated with a lower incidence of coronary artery disease and increase longevity (25), (26).

In a secondary analysis of PREvención con DIeta MEDiterránea trial involving 4,449 older adults at high cardiovascular risk (not selected with regards to gout), higher Mediterranean diet scores were associated with lower likelihood of having hyperuricemia (27). On the

other hand, in a secondary analysis of the Dietary Intervention Randomized Controlled Trial (DIRECT) involving 235 obese individuals, there was no difference in serum urate reduction among patients assigned to low-fat, restricted-calorie; Mediterranean, restricted-calorie; or low-carbohydrate, non-restricted-calorie diet over two years, including among in those with baseline hyperuricemia (28). Overall, serum urate decreased by approximately 0.4 mg/dL (baseline mean serum urate ± SD of 6.2 ± 1.3 mg/dL), 0.2mg/dL (baseline mean serum urate ± SD 6.0 ± 1.5 mg/dL), and 0.3mg/dL (baseline mean serum urate ± SD 6.0 ± 1.5 mg/dL) in the 3 groups, respectively. This indicates that the Mediterranean diet does not have substantial urate-lowering effects when compared with other diets. In the meta-analysis by Major et al., the DASH diet explained 0.28% variance in serum urate as compared to 0.06% for the Mediterranean diet, unadjusted for a genetic risk score (14). Though the effects of both diets on serum urate were small, the Mediterranean diet was concluded to be inferior to the DASH diet in reducing serum urate levels. Studies of the Mediterranean diet among people with gout have not yet been conducted, and thus the effects on flares and tophi are not known.

Other effects of the Mediterranean diet, such as its beneficial effects on cardiovascular disease and incident type 2 diabetes (25, 29), could potentially provide some rationale for its consideration in people with gout who have additional relevant comorbidities, much as the DASH diet may be appropriate for individuals with hypertension, and hyperlipidemia for example.

Similar to the DASH diet, the 2020 ACR guideline for the management of gout does not make specific recommendations about the Mediterranean diet as due to overall low quality of evidence, and lack of data among people with gout.(23)

Low Purine Diet:

A low purine diet consists of avoiding foods rich in purines, thus theoretically decreasing the end-product of purine metabolism in humans – urate. This diet recommends avoidance of foods that are rich in purines such as shellfish, organ meats, alcoholic beverages and canned fish such as sardines amongst others. Though low purine diets have been recommended for the management of gout, data regarding its efficacy on gout outcomes are lacking. Further, low purine diets are unpalatable, difficult to sustain, and reduction or elimination of purines leads to substitution with other dietary components; often in Western diets this may lead to compensatory higher consumption of carbohydrates and fats. Further, mean serum urate is thought to decrease by about 1 mg/dL with low purine diet thus still necessitating urate lowering therapy to achieve goal uric acid despite a strict diet. Among people without gout, purine-rich food intake has been associated with both increase in serum urate and risk of incident gout (30, 31). For example, in the Health Professionals Follow-Up Study, men in the highest quintile of meat intake compared to lowest quintile of meat intake had 1.41 times the risk of developing gout (95% CI 1.07, 1.86; p for trend = 0.02).

In terms of the impact of lowering purine intake on serum urate among people with gout, a small retrospective study involving 40 patients who were obese and had gout reported that those who underwent sleeve gastrectomy followed by a low purine diet for 12 months had

significantly greater reduction in serum urate, lower frequency of gout flares and less use of allopurinol than those who had a normal purine diet (32).

Gout flares have also been studied in relation to purine intake. In a self-controlled online case-crossover study, 633 participants reported dietary intake and other exposures in the two-day period preceding a gout flare as well as a two-day period at a time that was free of gout flares (33). Purine intake increased the risk of gout flares by five-fold; the effect persisted across subgroups by gender, alcohol use and drugs such as diuretics, allopurinol, NSAIDs and colchicine. Importantly, the risk was primarily limited to animal sources of purine rather than plant sources.

While short-term exposure to a purine rich diet may increase risk of recurrent gout flares, effects of longer-term reductions in purines on tophi and serum urate among people with gout are not known. The 2020 ACR guideline for the management of gout conditionally recommends limiting purine intake regardless of disease activity (23).

Role of Weight Loss:

Obesity is highly prevalent worldwide, with 1.9 billion adults reported to be overweight or obese.(34) Greater BMI is associated with increased risk of hyperuricemia and gout in a variety of studies (17). In the Normative Aging Study, an increase in weight was associated with an increase in serum urate over time, though they also noted a general rise in serum urate over time even in people without weight gain; nonetheless, weight gain was the strongest factor associated with rise in serum urate beyond the baseline urate level (35). These observations regarding serum urate have been supplemented by observations regarding risk of incident gout in men and women. For example, the Health Professionals Follow-Up Study reported that adiposity and weight gain were risk factors for incident gout among men (36). In the Taiwan National Health Insurance database involving 1189 patients observed over 6.45 years, obesity (BMI > 27) was an independent risk factor for incident gout among women with and without hyperuricemia (37). In another cohort study, obesity was a risk factor for incident gout but not for the recurrent gout flares (38).

Relatively fewer studies have reported on effects of weight loss on gout risk. In the Health Professionals Follow-Up Study, weight loss was associated with a lower risk of incident gout over a 12-year period of follow-up (36). In an example of the impact of greater degrees of weight loss, 1982 people who underwent bariatric surgery had a lower incidence of gout than 1999 people who were obese but who did not undergo bariatric surgery over a median of 19 years of follow-up (39). A 2019 meta-analysis included 20 studies with over 5000 patients to assess the relation of bariatric surgery to gout and serum urate. Most of the studies analyzed had at least a 12-month follow-up period. Across these studies, there was a mean serum urate decrease of 0.73 mg/dL at the third post-operative month, with ongoing sustained mean decrease of 1.91 mg/dL at 3 years post-operatively (pre-operative mean serum urate level 6.5 (5.7–7.2 95% CI) mg/dL) (40).

Data regarding impact of weight loss among people with gout was summarized in a 2017 systemic review of 10 longitudinal studies assessed impact of weight loss in overweight and

obese individuals with gout (41). Six studies showed beneficial effects of weight loss on gout flares and two studies demonstrated dose response relationship between weight loss and serum urate as well as gout flares. In a retrospective analysis of 147 people with obesity who underwent bariatric surgery, 67 patients without gout or hyperuricemia had a baseline urate of 5.41 (95% CI 5.13, 5.69) mg/dl. This group showed a mean decline in serum urate of 0.46 (95% CI 0.21, 0.71) mg/dl at the end of 12 months. A subset of 55 patients with hyperuricemia, who had a mean baseline serum urate of 8.01 (95% CI 7.6, 8.42) mg/dl showed a reduction in mean serum urate of 1.68 (95% CI 1.09, 2.25) mg/dl and the 25 participants in the study who had gout and a mean baseline serum urate of 9.15 (95% CI 8.29, 10.01), showed a reduction of 2.75 (95% CI 1.75, 3.75) mg/dl at the end of the 12 month study period.(42)

Another small retrospective study of patients with gout undergoing bariatric surgery also reported a decrease in serum urate and gout flares (43). In this study, 99 patients with gout who underwent bariatric surgery were compared to 56 patients with gout who did not undergo surgery. Patients who underwent bariatric surgery had a higher incidence of gout flares in the first post-operative month (17.5% of the surgery group vs 1.8% in control group), but in the subsequent 12 months, gout flares decreased significantly more in the bariatric surgery group than in the controls (23.8% pre-operatively to 8% post-operatively in the bariatric surgery group vs. 18.2% to 11.1% in controls over the same time period). The bariatric surgery group was also noted to have a significant reduction in serum urate (mean ± SD 9.1 ± 2.0 mg/dL at baseline for the bariatric surgery group vs. 5.6 ± 2.5 mg/dL, 13 months after bariatric surgery), whereas the control group did not change significantly (7.7 ± 2.0 mg/dL at baseline in the control group vs. 7.0 ± 1.6 mg/dL 13 months later).

Thus, weight loss appears to have beneficial effects on preventing incident gout, reducing serum urate, and decreasing flare frequency. These findings are also consistent with the studies above that have evaluated the relative contributions of diet and genetics in which weight was consistently identified as a key determinant of serum urate levels (44).

The 2020 ACR gout treatment guideline conditionally recommends using a weight loss program (no specific program endorsed) for people with gout who are obese or overweight, regardless of disease activity (23).

Role of Individual Foods:

Over the last several decades, various food items have been studied for their effects on hyperuricemia primarily, with limited studies regarding impact on gout outcomes. Here, we review alcohol, caffeine, cherry, dairy, high-fructose corn syrup, omega-3 fatty acids, and vitamin C.

Alcohol

Alcohol has long been anecdotally associated with gout, with well-established links to hyperuricemia, though data regarding specific types of alcohol remain mixed. The third NHANES survey, which included 14,809 participants, noted serum urate increased significantly with increasing beer or liquor intake, but not with wine intake (45). The Health

Professionals Follow-Up Study, which included 47,150 male participants who were free of gout, also reported that alcohol intake was significantly associated with an increased risk of gout, with beer (RR per serving per day 1.49, 95% CI 1.32 – 1.70) conferring a larger risk than spirits (RR per serving per day 1.15, 95% CI 1.04 – 1.28). However, they did not observe an increased risk with moderate wine consumption (RR per serving per day 1.04, 95% CI 0.88 – 1.22) (46).

Few studies have examined the effects of alcohol among people with gout. In a small study of patients with gout, which included 21 heavy drinkers (30 units or more per week), 8 moderate drinkers (less than 20 units per week) and 9 patients who seldom consumed alcohol or did not consume alcohol at all (47), serum urate among patients who limited or abstained from alcohol was 1.6 mg/dL lower than those who did not, and poor response to allopurinol was noted in patients with heavy alcohol consumption, as evidenced by multiple gout flares. The authors concluded that these effects were likely a combination of poor adherence to allopurinol and the hyperuricemic effects of alcohol. A self-controlled case-crossover study that included 724 participants with gout noted that increased alcohol consumption was associated with an increased risk of gout flares, with flares being 1.36 times higher in people who consumed 1–2 units of alcohol and 1.51 times higher in people who consumed more than 2–4 units of alcohol compared with times when they had no alcohol consumption in the prior 24 hours (48). Of note, all types of alcoholic beverages, including beer, hard liquor, and wine, were associated with increased risk of flares. No studies to date have provided insights regarding the relation of alcohol intake and tophi.

In recognition of the data from these observational studies, the 2020 ACR guideline for the management of gout conditionally recommends limiting alcohol intake in gout patients regardless of disease activity (23).

Caffeine, Coffee, Tea:

The third NHANES survey (1988 – 1994) data were also examined to study the relationship between coffee, tea and caffeine on serum urate (49). People who consumed 4 to 5 and > 6 cups of coffee had lower serum urate than that associated with no intake of coffee by 0.26 mg/dL and 0.43 mg/dL, respectively (baseline mean serum urate was 5.32 mg/dL). There was also a significant inverse association between decaffeinated coffee and serum urate. However, tea and total caffeine intake (i.e., taking all caffeine sources into account – coffee, tea, and cola) were not associated with serum urate. A study in Japanese participants also demonstrated an inverse association between coffee consumption and serum urate but no association with tea (50). In the Health Professionals Follow-Up Study, a validated food frequency questionnaire was used to assess intake of coffee, decaffeinated coffee, tea and total caffeine in 45,869 men free of gout (51). During the 12-year follow up period of the study, 757 new cases of gout were documented. Increasing coffee intake was significantly inversely associated with risk of gout. Decaffeinated coffee was also significantly inversely associated with risk of gout, while tea and total caffeine intake were not associated, similar to the findings for serum urate. Another study examined the association of coffee, tea, and total caffeine intake using a validated questionnaire with risk of gout in the Nurse's Health Study (52). Over the 26-year follow-up of 89,433 female participants, 896 cases of gout

were confirmed. The risk of gout was 22% lower with a coffee intake of 1–3 cups/day and 57% lower with intake of > 4 cups per day compared with individuals who did not drink coffee. Decaffeinated coffee > 1 cup per day was also inversely associated with risk of gout. Tea again showed no association with gout. The mechanisms behind these associations however remain unclear.

There are no published studies to date on caffeine intake in patients with gout to assess effects on flares and tophi. Of note, caffeine has a chemical structure similar to allopurinol, and thus merits further evaluation in patients with gout.

The 2020 ACR guideline for the management of gout does not make any recommendations regarding coffee, tea or caffeine intake.

Cherries/Cherry Juice Concentrate:

Cherries are purported to have antioxidant properties that may have a role in reducing the acute inflammatory response to monosodium urate crystals, and may potentially have a uricosuric effect (53).

A crossover, randomized, placebo controlled trial of 26 overweight and obese individuals (BMI > 25 kg/m^2) without gout reported a reduction in serum urate by 19.2% in the tart cherry juice arm vs. an increase in the placebo arm (54). The mean serum urate at baseline was 6.3 mg/dL with an absolute decrease of approximately 1 mg/dL in the tart cherry juice arm. However, in a RCT of 50 patients with gout (half on allopurinol and half on no ULT) who were randomized to placebo or varying doses of tart cherry concentrate for 28 days, there was no significant effect of cherry on serum urate levels. The authors concluded that any favorable effect of cherries on gout flares may not be mediated by reduction in serum urate (55).

The previously mentioned online case-crossover study also evaluated the effects of cherry intake on gout flares (56). Cherry intake among 633 individuals with gout over a 2-day period was associated with a 35% lower risk of gout flares compared with periods of no cherry intake. The effect persisted after adjusting for known risk factors for gout flares and anti-gout medications.

Given the small number of participants in these studies and the differing findings, potentially related to differences between people with versus without gout, there are insufficient data to draw specific conclusions about cherry intake and gout.

Citing the lack of sufficient data, the 2020 ACR guideline for the management of gout does not make a specific recommendation regarding cherries/cherry juice concentrate (23).

Dairy:

In population-based studies in individuals without a diagnosis of gout, higher consumption of dairy products has been associated with a lower risk of gout and with lower serum urate (31, 57). This was attributed to a possible hypouricemic effect from dairy products. An *In vitro* study demonstrated that dairy factors such as GMP and G600 milk fat extract inhibit

Interleukin 1β and thus may have a role in preventing gout by preventing the inflammatory response to monosodium urate (MSU) crystals (58). Subsequently, a randomized controlled crossover trial was conducted to study these findings clinically. In this trial, 16 male participants, without a history of gout, received 80 grams of protein from a soy control, from early and late season skim milk (late season skim milk is rich in orotic acid, which is a uricosuric agent) and ultra-filtered milk protein isolate-85 (MPI-85) (59). Serum urate decreased by 10% in all the milk groups over a 3-hour period, thought to be secondary to increased excretion of urate. In comparison, urate increased by 10% in the soy group. Following that study, 120 participants with gout and recurrent flares were enrolled in a RCT, and randomized to lactose powder control, skim milk powder (SMP), or SMP with glycomacropeptide (GMP) and G600 (60). There was a reduction in the frequency of gout flares in all three groups with a significant reduction in gout flares in the SMP/GMP/G600 group when compared to the other 2 groups. Because of the limited data regarding common dairy products in people with gout, the 2020 ACR treatment guideline refrained from making a recommendation regarding dairy protein intake (23).

High Fructose Corn Syrup:

In a small metabolic study involving 17 subjects (6 adults without gout, 6 patients with gout and 5 children of patients with gout), the acute effects of fructose were demonstrated, with average serum urate rising by 1–2mg/dL within 2 hours of ingestion of 1 g fructose per Kg body weight (61). Longer term effects on serum urate have also been noted. In the Third National Health and Nutrition Examination Survey (1988 to 1994), sugar-sweetened beverage consumption was associated with higher serum urate levels (62). High-fructose corn syrup has also been associated with increased risk of incident gout in both the Nurses' Health Study and the Health Professionals Follow-Up Study (63) (64).

There are no published data on the effects of high fructose corn syrup consumption on tophi and flares among patients with an established diagnosis of gout.

The 2020 ACR guideline for the management of gout conditionally recommended limiting high fructose corn syrup intake regardless of disease activity (23).

Omega-3 Fatty Acids:

Omega-3 (or n-3) polyunsaturated fatty acids (PUFA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are thought to have anti-inflammatory properties. They inhibit NALP-3 inflammasome assembly and neutrophil chemotaxis among other factors that cause an inflammatory response to MSU crystals (65). *In vitro* data also support the potential for omega-3 PUFA to act as URAT1 inhibitors (66) Limited data are available regarding effects of omega-3 PUFA on serum urate. A small randomized controlled trial in 30 young healthy adults showed that daily intake of fish oil (2 g; primarily DHA and EPA) resulted in a significant decrease of SUA after 4 and 8 weeks of supplementation (67). Studies to date have not reported on impact of omega-3 PUFA intake on risk of incident gout.

In terms of potential effects among people with gout, a study of 112 men with gout noted a significant trend for a negative association between serum levels of omega-3 PUFA and gout flares in the preceding 12 months,(65) though the study was unable to account for other

dietary factors. In the online case crossover study discussed above, among 724 participants with gout, omega-3 PUFA-rich fish consumption of at least 2 servings in the prior 48 hours was associated with a 26% lower risk of gout flares compared with time periods of no consumption when adjusted for concomitant purine intake (68). Self-directed n-3 PUFA supplementation such as with fish oil or cod liver oil was not associated with a lower risk of gout flares, though few reported supplement use and doses may be too low for anti-inflammatory effects (68). Thus, only limited data exist to date regarding potential favorable effects of omega-3 fatty acids in gout. The 2020 ACR guideline for the management of gout does not comment on omega – 3 fatty acids and gout.

Vitamin C:

Data on vitamin C and serum urate levels are mixed, primarily related to the populations studied. Some older studies have shown varying degrees of uricosuria with vitamin C, leading to recommendations to add vitamin C to the diet to help lower serum urate (69, 70). However, these studies were conducted among people without gout who had normal renal function, with large doses of Vitamin C and in small numbers of participants. It should be noted that higher doses of vitamin C with its purported uricosuric effects could be a concern for renal urate over-excretors with regards to nephrolithiasis. A 2011 meta-analysis of RCTs which included 556 patients without gout in which a median dose of 500 mg/day was associated with a statistically significant but minor reduction in serum urate (0.35 mg/dL) (71). A prospective study looking at 46,994 male participants, with no history of gout at baseline, reported that higher vitamin C intake was independently associated with a lower risk of gout.(72) A small pilot RCT reported clinically insignificant effect of 500mg/d of supplemental vitamin C versus placebo on serum urate in people with gout, regardless of concomitant allopurinol administration (73).

Data regarding effect of vitamin C in people with gout were considered to be insufficient to support recommendation of vitamin C use in patients with gout by the 2020 the American College of Rheumatology’s Gout Guideline, and with the negative clinical trial in people with gout, a conditional recommendation against its use was made (23).

A summary of the associations of the various diets and dietary factors on serum urate (largely among people without gout), risk of incident gout among people free of gout, gout flares, and tophi, as well as related 2020 ACR gout treatment guideline recommendations, if any, are provided in Table 1.

Conclusion:

The available evidence regarding impact of diet on hyperuricemia and gout is largely limited to studies among people without gout. Various dietary approaches may have a small effect of serum urate levels, though for most patients with gout, these effects will be insufficient for adequate gout management and therefore can be considered only as adjunctive measures with pharmacologic therapy needing to be the mainstay of management to achieve the degree of urate-lowering needed to control gout disease activity. Given the importance of urate underexcretion in gout pathophysiology, and the modest impact of diet on serum urate, healthcare professionals should be mindful to avoid dialogue that results in patient blaming,

and rather support counseling for medication adherence and placing discussions regarding diet as adjunctive. However, for those that do not yet meet indications for urate-lowering therapy, some of these approaches may provide options for lowering serum urate modestly and potentially reducing risk of flares in some instances.

Studies, and preferably trials, in patients with gout are required to assess the effectiveness of various diets on clinically relevant gout outcomes such as flares and tophi. Simply extrapolating findings from general population samples to people with gout may not be wholly applicable, with vitamin C studies providing an example where findings in people with gout did not mirror the findings from people without gout. There are supportive observational data to suggest that flares may be impacted by alcohol and purines, particularly from animal sources, and that avoidance or limiting high fructose corn syrup may have other beneficial health effects. Weight loss appears to have benefits on reducing gout flares among people with gout, and also has numerous additional attendant health benefits. Thus, there may be benefits to dietary adjustments in certain individuals where excessive factors may be at play (including weight), but the data to date support the ongoing importance of pharmacologic management of gout as being foundational for optimal disease control.

Funding sources:

Dr. Neogi's work was supported by K24 AR070892 and P30 AR072571

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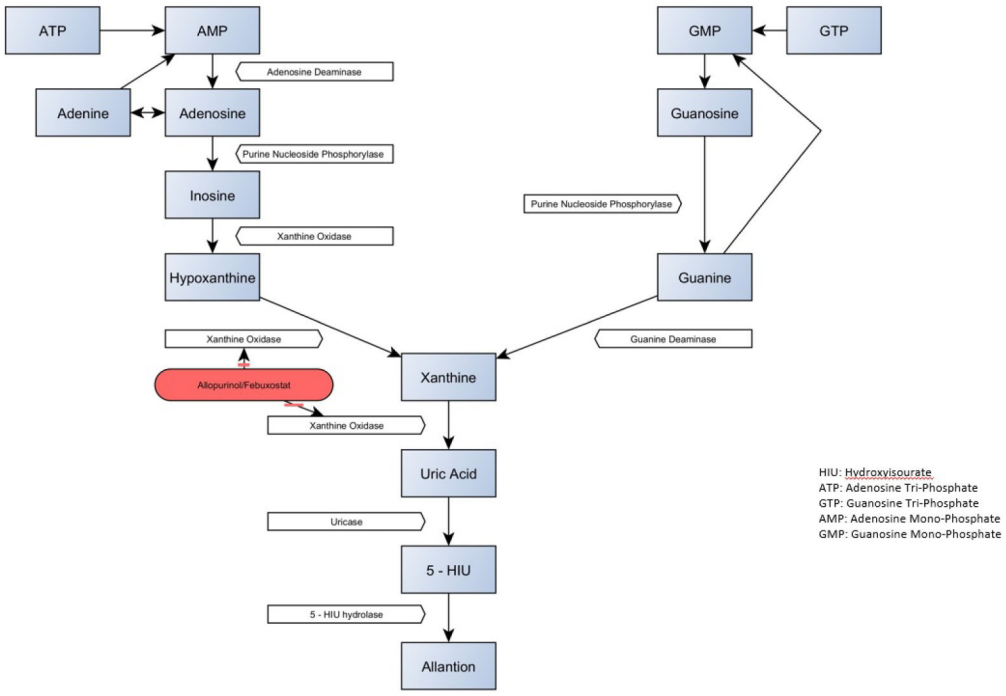

Figure 1:
Breakdown of purine to allantion Humans and higher primates lack uricase and are thus unable to convert uric acid to allantion

Table 1 -

Impact of diets and individual foods on urate levels, incident gout and gout flares

	Among people without gout*			
	Serum urate level	**Risk of incident gout**	**Risk of gout flares**	**ACR 2020 Gout guideline dietary recommendation**
Diet				
DASH Diet	↓	↓	No data	No recommendation
Mediterranean Diet	↓	Not enough data	No data	No recommendation
Purine Rich Diet	↑ (short-term)	↑	↑	Recommends limiting purine intake
Weight				
Obesity	↑	↑	No data	Conditionally recommends following a weight loss program (no specific type of program recommended)
Weight Gain	↑	↑	Not enough data	
Weight Loss	↓	↓	↓	
Individual Foods				
Alcohol	↑	↑	↑	Conditionally recommends limiting alcohol intake
Caffeine	↓	↓	No data	No recommendation
Cherries	Not enough data	Not enough data	↓	No recommendation
Dairy	↓	↓	↓	No recommendation
High-Fructose Corn Syrup	↑	↑	No data	Conditionally recommends limiting intake of high fructose corn syrup
Omega 3 Fatty Acids	Not enough data	Not enough data	Not enough data	No recommendation
Vitamin C	No effect (people with gout) May ↓ (people without gout)	Not enough data	Not enough data	Conditional recommendation against use

*Studies in people without gout unless otherwise specified