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Nutritional factors in the prevention and treatment of gout

Sebastian Tomaszuk¹, Karolina Wąsik¹, Magda Wojtuś¹

¹Medical University of Lublin, Aleje Racławickie Street 1, 20-059 Lublin, Poland

Sebastian Tomaszuk; sebastiantomaszuk@gmail.com;

ORCID 0000-0002-1572-5181;

Karolina Wąsik; wasik.karolina.0@gmail.com;

ORCID 0000-0003-2817-0848;

Magda Wojtuś; magdaawojtus@gmail.com;

ORCID 0000-0003-4299-2143

Summary:

Introduction and purpose:

Despite the fact that effective urate lowering therapy and anti-inflammatory drugs for the treatment of gout are commonly available, there is considerable interest in novel treatment approaches. Gouty patients often have a multitude of comorbidities, which lead to concern over drug–drug interactions and medication adverse events. Thus, diet modifications are examined as a way of nonpharmacological treatment of gout. In this review, we explore the potential impact of nutritional factors on hyperuricemia and clinical gout outcomes. A search was conducted using PubMed and Google Scholarship databases.

Brief description of the state of knowledge:

Management in patients with gout should be holistic. Incorrect nutrition may lead to hyperuricemia. Studies to date suggest that avoidance of certain foods and beverages can decrease the frequency of gout flares. Weight loss may be beneficial for prevention as well as treatment of gout and its comorbidities. The impact of various types of diet on the course of gout has been given particular attention and recent research suggests that vegetarian, mediterranean and dash diets may be beneficial for gouty patients. Also, some vitamins and omega-3 PUFA have favorable effects and the potential clinical use in gout treatment.

Conclusions:

We propose that simple dietary regimens may be beneficial to complement therapeutic management or contribute to the prevention of flares in gout patients. Although piecemeal modifications of various nutrients often provide incomplete dietary recommendations, understanding the role of nutritional factors in gout development would be helpful for patients in choosing their healthy diet.

Key words: gout; hyperuricemia; nutritional factors; non-pharmacological treatment; health

1. Introduction

Gout is a very common disease that is relatively very widespread around the world especially in developed countries. In the USA approximately 3.9% of adults suffer from it and its occurrence is constantly rising. People suffering from obesity, with metabolic syndrome and men over 40 years old are especially at risk to develop it [1].

Most often, the clinical manifestations of gout might include: intense joint pain of the toe (usually affects the first metatarsophalangeal joint, but any joint might be affected), lingering discomfort, inflammation and redness of joints, and limited range of motion. Symptoms usually appear early in the morning. Gout manifests itself not only in joints. In the course of gout also might be identified: tophi, kidney failure, kidney stones and hypertension [2,3].

The pathogenesis of the gout is deposition of sodium urate crystals in the joints and in the subcutaneous tissue, which causes the symptoms of the disease. Sodium urate crystals crystallize when uric acid level in the blood is high. This is often due to triggers such as: alcohol, large amounts of purine-containing foods (especially meat), exercise, injury, surgery, infections and medications (especially thiazide diuretics) [4]. First-line treatment of a gout attack are non-steroidal anti-inflammatory drugs (NSAIDs) and after an acute attack of the gout the allopurinol can be used in prophylaxis [5].

2. State of knowledge

2.1 The role of diet and dietary recommendations in gout.

Purines are molecules compounded by pyrimidine and imidazole rings.

They are converted to hypoxanthine by the xanthine oxidase enzyme (XO) after intake, and then to xanthine and uric acid. Therefore, a special role in the gout pathogenesis is attributed to diet. It should be selected according to the needs of the patient (age, weight, vitamin deficiencies) and should contain all the necessary macro and microelements.

Healthy Eating Pyramid is the visualization of how a healthy diet should be well-balanced. There is a variation that can be useful for patients suffering from gout. According to it, the diet should include whole grain foods and plant oils at most meals. The least frequent group of products which should be consumed only sparingly are red meat, sweets and refined carbohydrates [6]. Incorrect diet may contain excess purines leading to hyperuricemia. Foods that are rich in purines are mainly meat and high protein vegetables. However, the influence of the consumption of high protein vegetables on hyperuricemia in recent years is undermined.

A cross-sectional research made by Aihemaitijiang et al. studied the effect of a purine-rich diet in Chinese adults. In the results purine-rich vegetables did not correlate with hyperuricemia [7]. Such outcomes can be explained by other substances that are contained in plants. These compounds such as vitamin C might potentially increase the excretion of uric acid from the body. Research in this direction is still needed, but they are increasingly included in dietary recommendations.

As meta-analysis by Li et al. revealed the consumption of red meat, seafoods, alcohol or fructose was associated with higher gout risk. Also in this study, the results indicated that the high-purine vegetables diet did not lead to hyperuricemia [8]. Additionally cocoa, fish and yeast can contribute to the occurrence of an increased amount of uric acid in the blood, and therefore their consumption should be limited.

Dietary recommendations do not apply only to solid foods, but also refer to liquids. The effect of drinking tea on gout is not clear and depends on the type of tea. Nonspecific types of tea in study did not affect the higher risk of gout [9]. However, the daily drinking of green tea increases the level of uric acid in the serum [10]. Alcohol, due to the fact that it increases the conversion of purines to uric acid, is not recommended in the diet and people suffering from gout should avoid it [11]. Also, fructose-sweetened beverages should be limited. It is worth mentioning that from the 2021 meta-analysis made by Ayoub-Charette et al. sugar-sweetened beverages (SSBs) increase uric acid levels in the blood, however consumption of 100% fruit juice decreased uric acid level [12]. Another drink that has shown a beneficial effect on reducing the amount of uric acid in the blood is water with vitamin C. It happens as a result of vitamin C competing with urate for renal reabsorption [13,14]. In addition, coffee, milk and yogurts also showed such an effect. All of them were associated with lower risk of gout [10]. Also drinking milk and yogurt have a lowering effect on uric acid levels in serum [15]. Diet should be multifaceted and focused on the treatment of comorbidities such as hypertensive, dyslipidemia, metabolic syndrome and especially obesity which often coexist with gout. Dietary recommendations should not only contain qualitative advice. A caloric deficit should be considered and induce weight loss in patients with increased BMI. The results from meta-analysis from 2022 which was focused on modifiable risk factors and incidence of gout clearly show that increasing BMI was correlated with the higher risk of gout [16]. The diet should consist of regular meals, adequate fluid intake and should be accepted and strictly followed by the patient as the most important.

2.2 Vegetarian diet in the treatment of gout

When it comes to the influence of the vegetarian diet on symptoms of gout, scientific data is composite. Outcome of this diet strategy is dependent on the composition of the diet as it is known that some plant based foods also contain high purine levels [17]. Siener et al. proved that vegetarian diet decreased the risk of uric acid crystallization by 93% when compared to the standard western diet. The type of vegetarian diet was ovo-lacto-vegetarian- it excludes not only meat, but also eggs [18]. This strategy is also supported by two prospective cohort studies conducted by Chiu et al. In this paper lacto-ovo-vegetarians noted the lowest uric acid level out of the three groups- other two were vegans and nonvegetarians [19]. Vegetarian strategy seems to be one of the most beneficial as in a study made by Schmidt et al. serum uric acid level was the lowest in this group while vegans noted the highest level followed by meat eaters [20].

2.3 Ketogenic diet in the treatment of gout

Ketogenic diet is based mainly on high-fat meals with moderate dose of proteins and very limited amount of carbohydrates [21]. Currently, its possible health properties among many diseases are being investigated. As stated by Goldberg et al. in their study proved that a ketogenic diet increases the production of β -hydroxybutyrate (BHB). This molecule shows anti-inflammatory properties, therefore could potentially alleviate the symptoms of gout [22]. Although it still remains unclear and questionable if ketogenic diet may be considered as beneficial for patients with gout as ketosis that is induced by this way of nutrition may lead to a higher uric acid level [23].

2.4 Dash diet in the treatment of gout

Dash diet is a proven health-promoting way of eating that is grounded on high consumption of vegetables and fruits, legumes, nuts and seeds and low-fat dairy. There is also a strong emphasis on limiting the consumption of sodium, sugar and saturated fats [24]. This dietary pattern among many health benefits is associated not only with the lower risk of gout as prospective cohort study conducted on men investigated [25], but its benefits were also observed among patients who already have gout and were at a time not during pharmacological urate lowering therapy (ULT). The outcome suggested that this strategy may be a useful tool to lower the urate serum level [26]. This evidence is also supported by another study which compared a dash diet to standard diet and one with higher vegetables and fruits consumption, but without other restriction. Dash diet turned out to be the most beneficial in reducing serum urate levels [27].

It is also known that gout is often part of the metabolic syndrome and is associated with insulin resistance. Dash diet is proven to exert a positive impact on this condition and is profitable for patients who apart from metabolic symptoms want to improve the tenor of gout [6].

2.5 Mediterranean diet in the treatment of gout

This model of nutrition concentrates on the higher consumption of antioxidant rich extra virgin olive oil, fruits, cereals, nuts and legumes, moderate use of fish and other meat, dairy products and red wine with the determined frequency [28]. This diet pattern is widely recognised for its beneficial effects, therefore its impact on gout disease is also being observed. It is known that long term usage of this model is connected with lower serum uric acid level in elderly individuals, although Ikarian study demonstrated that only in male cases, therefore may be considered as a part of preventative lifestyle [29]. This model was also being investigated among patients who already have gout and in a review published by Theodoridis et al. authors concluded that this diet may be potentially helpful in the treatment of gout, because its components in a large part are proven to have positive effects on serum uric acid level. It was noted that further research is still needed [30].

2.6 High-protein diet in the treatment of gout

The association between high protein intake and gout remains characterized as negative. As study by Xi et al highlighted, incidence of gout increased in a group with this diet pattern [31]. This consumption pattern compounded not only serum concentrations of uric acid, but also renal function [32]. Also in an animal model high protein diet escalated the level of serum urate [33]. Although, consuming more protein on a weight loss diet has been shown as beneficial in a pilot study by Dessein et al. During this study participants who already had gout attacks in the past have consumed 30% of calories from protein on a 1600 kcal. This strategy resulted in fewer gout attacks and lower uric acid level [34].

2.7 Vitamin supplementation in the treatment of gout

Although many epidemiological studies indicate a significant correlation between high vitamin C intake and lower serum uric acid levels, data is still mixed and primarily related to the populations studied [35,36]. Pharmacologically, the uricosuric effects of vitamin C seem to have the highest impact on hyperuricemia. Both uric acid and vitamin C can be reabsorbed in the proximal tube via anion-exchange transport. Vitamin C overload can competitively suppress the reabsorption of uric acid in the filtrate [37]. The uricosuric function of vitamin C is also connected with downregulation of URAT1 activity and/or Na⁺-dependent anion cotransporter could promote uric acid excretion [35]. The reports about vitamin C-caused reduction in serum urate and association between high doses vitamin C intake and a lower risk of gout have caused recommendations to add vitamin C to the diet to reduce serum uric acid levels [35,38,39]. However, it should be noted that these studies were conducted with high vitamin C doses among small numbers of participants without gout [38,39]. In contrast, a small pilot randomized controlled trial revealed clinically insignificant effect of 500mg/d of supplemental vitamin C placebo on serum urate in people with gout, regardless of concomitant allopurinol administration [40]. In consequence, in 2020 the American College of Rheumatology's (ACR) Gout Guideline made a conditional recommendation against use of vitamin C in people with gout [41].

Just like vitamin C, vitamin A and vitamin E also show beneficial effects against oxidative stress and inflammation, as well as effectively decreasing serum uric acid (SUA) levels [42]. The cross-sectional study evaluated the association of dietary vitamin E intake with hyperuricemia in US adults. The results indicated that it was negatively correlated with hyperuricemia, especially among males and participants aged ≥ 60 years [43]. Uric acid-lowering effect might be also observed in a vitamin D-rich diet. In provided by Charoenngam meta-analysis of seven cross-sectional studies, individuals with vitamin D deficiency and insufficiency have been shown to have increased serum uric acid in a dose-dependent manner compared with vitamin D-sufficient individuals (pooled mean differences 0.45 and 0.33 mg/dL). These results are thought to be associated not only with the fact both vitamin D deficiency/insufficiency and hyperuricemia share common comorbidities such as obesity and metabolic syndrome, but also to a direct causal association between the two conditions [44]. These conclusions were also supported by the study conducted on 71 participants with prediabetes randomized to receive weekly doses of 20,000 IUs of vitamin D2, 15,000 IUs of vitamin D3 or no vitamin D. In this paper vitamin D supplementation was associated with a reduction in mean serum uric acid level by 0.6 mg/dL in those with baseline uric acid level of >6 mg/dL [45]. This effect is suggested to be caused by PTH suppression [46]. However, despite the causal link between vitamin D and uric acid, no association with gout has been demonstrated [47].

2.8 Minerals supplementation in the treatment of gout

As it is commonly known dietary potassium intake has diuretic and natriuretic effects and even a minor potassium insufficiency can trigger an impairment in the kidney's capacity to secrete sodium chloride and retain sodium [48], which results in renal dysfunction. Whereas long-term routine potassium replenishment causes thiazide mediated by thiazide diuretic elevation of uric acid [49]. Moreover, a similar facilitation effect was described by Martelin et al. when iron accumulation triggers increased XO activity. In this study ferric ammonium citrate and FeSO₄ elevated intracellular iron levels and elevated XO activity in mouse fibroblast and human bronchial epithelial cells [50]. However, the later analysis conducted by Cheng showed a significant negative correlation between iron and magnesium with the risk of gout [51]. It should be also noticed that minerals have a crucial role in maintaining acid-base balance and low urine pH predisposes to acid stone formation. Hypercalciuria is a risk factor for calcium stone disease and in this light the level of calcium also affects the serum uric acid concentration by causing a uric acid excretion disorder [52]. Normal calcium intake can be beneficial because of decreasing the potential risk of kidney stone formation and conducting uric acid elimination in renal tissue [53,54].

2.9 Omega-3 Fatty Acids supplementation in the treatment of gout

Omega-3 polyunsaturated fatty acids (PUFA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) potentially have anti-inflammatory properties. They can inhibit NALP-3 inflammasome assembly and neutrophil chemotaxis among other factors that lead to an inflammatory response to monosodium urate crystals [55]. Yan et al. showed that stimulation of macrophages with omega-3 PUFA abolished NLRP3 inflammasome activation and inhibited subsequent caspase-1 activation and IL-1 β secretion. Through this mechanism omega-3 PUFA can repress inflammation and prevent inflammation-driven diseases, so its use may have the potential clinical use in gout treatment [56]. Data regarding effects of omega-3 PUFA on serum urate are limited. A randomized controlled trial conducted on 30 young healthy adults revealed 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 [57].

A study with 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, though other dietary factors were unable to account [56]. Also in the online case crossover study 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 [58]. However, there was no association between self-directed omega-3 PUFA supplementation such as with fish oil or cod liver oil and a lower risk of gout flares, though few reported supplement use and doses may be too low for anti-inflammatory effects [58]. Because of limited data regarding potential favorable effects of omega-3 PUFA in gout, 2020 ACR guideline for the management of gout does not comment on omega-3 PUFA and gout [41].

2.10 Cherries supplementation in the treatment of gout

In traditional reputation consumption of cherries or cherry juice alleviates pain in arthritis and gout. A growing body of literature shows that cherries may have anti-inflammatory, antioxidant and pain-mediating effects because of their phenolic compounds [59]. Potentially cherries may also have a uricosuric effect [60]. Since consumption of cherries or cherry juice decreased CRP and oxidative stress, and increased total antioxidant capacity, it was suggested that such effects might provide symptom relief in patients with gout [59]. A crossover trial with 26 overweight and obese participants without gout revealed a reduction in serum urate by 19.2% in the tart cherry juice arm vs. an increase in the placebo group. The tart cherry juice intake resulted in an absolute decrease of approximately 1 mg/dL serum urate, while at baseline its mean value was 6.3 mg/dL [61]. In contrast, in the study conducted by Stamp et al. in patients with gout (half on allopurinol and half on no ULT), who were given placebo or varying doses of tart cherry concentrate for 28 days, there was no significant effect of cherry on serum urate levels [62]. Other work, evaluating the effects of cherry intake on gout flares among 633 individuals with gout, who consumed cherries over a 2-day period, revealed a 35% lower risk of gout flares compared with periods of no cherry intake. The effect could be sustained thanks to adjusting for known risk factors for gout flares and anti-gout medications [63].

However, due to insufficient data, the 2020 ACR guideline for the management of gout does not make a specific recommendation regarding cherries/cherry juice concentrate intake [42].

3. Conclusions

Gout is a diet-dependent disease to a certain extent and science acknowledges that the nourishment pattern has an impact on the tenor of it. Nutritional advice that may moderate the course of disease are mostly not very strict and do not differ from the average healthy diet that every human should follow in order to stay healthy. However, the degree of this dietetic influence remains unknown. Patients affected with gout should focus on reducing nutritional risk factors for this disease and consider appropriate supplementation.

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