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RISK FACTOR FOR GOUT AND PREVENTION : A SYSTEMATIC REVIEW

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Abstract

Due to the supersaturation of uric acid, monosodium urate monohydrate crystals accumulate in the tissues, causing gout. Gout is characterized by elevated serum urate levels, acute gouty arthritic episodes, the production of tophi, gouty nephropathy, and uric acid stones. Until now there is no definite percentage/number of people with gout arthritis in the world, due to differences in research sampling methods in determining the number of sufferers of this disease. However, especially in America, there has been a significant increase in cases of gouty arthritis in the last 10 years. Uric acid is a waste product created by the body when renewing cells of gout patients produce more uric acid in the body and the body is unable to eliminate uric acid through urine, causing uric acid to accumulate in the blood. Significant roles are played by genetics, gender, and diet (alcohol intake, obesity) in the development of gout. The underlying cause of hyperuricemia determines the elements that lead to the development of gout. A diet heavy in purines can precipitate gout episodes in individuals with congenital defects in purine metabolism that result in elevated uric acid generation. Many risk factors for gout have been identified via research, including alcohol risk behavior (only in males), body mass index, estimated glomerular filtration rate, triglycerides, and triglyceride levels. Gout sufferers should avoid uric acid-raising meals and beverages. The patient drinks plenty of water. Gout sufferers should exercise regularly. To maintain weight, walk 150 minutes per week or 30 minutes each day. Avoid uric acid-raising medications like hydrochlorothiazide, aspirin, and cyclosporine.

Keyword: *Genetics; Gout, Kidney; Uric Acid; Tophy*

INTRODUCTION

Gout is a disease caused by the accumulation of monosodium urate monohydrate crystals in the tissues due to supersaturation of uric acid. Gout is characterized by increased serum urate levels, attacks of acute gouty arthritis, formation of tophus, gouty nephropathy and uric acid stones.[1] Tophus are solid-shaped nodules consisting of deposits of uric acid crystals that are hard, painless and present in joints or tissues. Tophus is a chronic complication of hyperuricemia due to the ability of urate to be eliminated is not as fast as its production. Tophus can appear in many places, including cartilage, synovial membrane, tendons, soft tissue and others.[2,3]

Manifestations of an acute attack of gout can be arthritis which occurs very quickly in a short time. The patient sleeps without any symptoms, then wakes up in the middle of the night due to such severe pain that he cannot walk. Symptoms are usually monoarticular with the main complaint being pain, swelling, feeling warm, red, with systemic symptoms of fever, chills, and feeling tired. In men, onset mainly occurs in the fourth to sixth decades, whereas in women, in the six to eight decades.[4,5]

Onset before the age of 30 years in a premenopausal woman should raise suspicion of an inherited enzyme defect, inherited or toxic kidney disease, or induced by drugs or other toxic agents. The most frequent location is MTP I which is usually called podagra. If the disease process continues, other joints can be affected, namely the wrists and feet, knees, fingers and elbows. These acute attacks heal spontaneously in a few days to a few weeks, multiple recurrences, can affect several joints. In mild acute attacks, complaints may disappear within hours or days. Severe attacks can last days to several weeks.[4,5]

To date, there is no definitive proportion or number of people with gout arthritis in the world due to variations in research sampling methodologies used to determine the number of sufferers. In the last ten years, however, there has been a dramatic increase in cases of gouty arthritis, particularly in the United States. There was an increase in the prevalence of gout patients from 2.9/1000 people in 1990 to 5.2/1000 people in 2010, with the majority of cases occurring in men with a peak age of > 75 years. This is primarily caused by primary gout, not subsequent gout.[6,7]

Uric acid is a waste product produced by the body when renewing cells of gout sufferers produce more uric acid in the body and the body is unable to remove uric acid through urine, causing uric acid to build in the blood. Genetics, gender, and nutrition (alcohol consumption, obesity) play significant roles in the development of gout. The factors that contribute to the development of gout depend on the underlying cause of hyperuricemia. A high-purine diet can trigger gout attacks in people who have congenital abnormalities in purine metabolism resulting in increased uric acid production.[7–9]

Various precipitating factors are considered responsible for the increased incidence of gout, including genetics, age over 45 years, obesity, metabolic syndrome, hypertension, diabetes and increased alcohol consumption. Genetic factors are familial factors that are passed from parents to their children. Genes that play a role in the emergence of gout include the SLC22A12 gene which functions to form the protein URAT1 which plays a role in the transportation of monossodium urate (MSU) in the body.[10]

The presence of polymorphisms in this gene causes excessive reabsorption in the renal tubules resulting in hyperuricemia. The SLC2A9 (GLUT9) gene is an important gene in the regulation of glucose and fructose transport in the body.[11] This gene also plays an important role in MSU reabsorption in the proximal tubule of the kidney and can cause hyperuricemia.[5,12] This article review some research on risk factor for gout and it prevention.

METHODS

This study followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 project standards for data collection, processing, and reporting. The adopted regulations were based on these concerns. This literature review examines risk factors for gout and its prevention. The key issues raised by the current study are as follows: 1) Articles must always be written in English and cover gout risk factors and prevention. 2) This review examined publications published after 2015 but within the scope of this systematic review's time limit. Editorials, submissions without a DOI, reviews of previously published articles, and entries that are substantially identical to those in the journal will not be included in the anthology.

The search for studies to be included in the systematic review was carried out from March, 20th 2023 using the PubMed and SagePub databases by inputting the words: “gout” and “risk factor”. Where *("risk factors"[MeSH Terms] OR ("risk"[All Fields] AND "factors"[All Fields]) OR "risk factors"[All Fields] OR ("risk"[All Fields] AND "factor"[All Fields]) OR "risk factor"[All Fields]) AND ("gout"[MeSH Terms] OR "gout"[All Fields])* is used as search keywords.

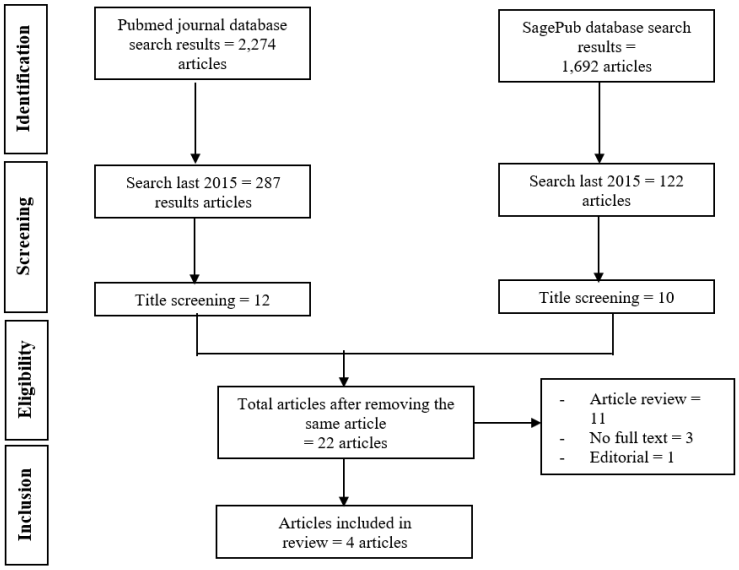

Figure 1. Article search flowchart

Each study's abstract and title were used to determine eligibility. Consequently, historical literature is their primary source. After reviewing multiple publications with identical results, submissions in unpublished English are sought. Only studies meeting inclusion criteria were included in the systematic review. This narrows the search results to only those that fit the specified parameters. Evaluation follows. In the study's analysis, authors, publication dates, location, activities, and parameters were listed. After saving search results in EndNote, duplicate articles were removed from the database. Two reviewers assessed the relevance of each article's title and abstract.

Before picking which manuscript to study, each author read the title and abstract of each publication. Following that, we'll go over all of the papers that match the inclusion requirements for the review. Following our investigation, we will examine pertinent research articles. This rule determines which manuscripts will be reviewed. It should be easier to choose which items to investigate further. Which earlier studies were incorporated into the review, and why?

RESULT

First study showed that gout was found to develop in 14.7% of men and 19.5% of women who had hyperuricemia (HU). With increasing baseline serum urate (SU) category, the age-adjusted HR in men increased from 2.7 to 6.4 and in women it increased from 4.4 to 13.1, and there was a statistically significant interaction of sex ($p < 0.001$) between the two factors. This was in comparison to subjects who were in the lowest SU category. At the beginning of the study, SU was strongly associated with factors such as body mass index, estimated glomerular filtration rate (negative), triglycerides, alcohol risk behavior (only in men), and comorbidities such as hypertension, cardiovascular disease, and diabetes. These factors were present in both sexes.

Table 1. The litelature include in this study

Author	Origin	Method	Sample	Conclusion
Kapetanovic, 2018	Sweden	Prospective study	1,275 individuals	Over a 30-year period, the absolute risk of developing clinically diagnosed gout was 3.8% in middle-aged subjects, and it increased progressively in both men and women in relation to baseline SU. This risk increase was significantly greater in women than in men, despite the fact that the associations between baseline risk markers and SU levels were similar in both sexes.
Wang, 2015[13]	United State of America (USA)	Retrospective cohort study	371 incident cases (231 men and 140 women) of gout	The findings of this study lend epidemiological support to the hypothesis that chronic kidney disease (CKD) is one of the risk factors for gout.
Yokose, 2020[14]	United State of America (USA)	Dietary Intervention Randomized Controlled Trial (DIRECT)	235 participants with moderate obesity randomly assigned to low-fat, restricted-calorie (n = 85); Mediterranean, restricted-calorie (n = 76); or low-carbohydrate, non–restricted-calorie (n = 74) diets	Diets that are focused on lowering nonpurines may improve SU and cardiovascular risk factors at the same time. This improvement is most likely mediated by a reduction in adiposity and insulin resistance. These dietary choices might give patients with customised routes that are tailored to their comorbidities and their preferences for adherence to treatment.
Choi, 2020[15]	United State of America (USA)	Retrospective cohort study	14,624 adults	In this study that was designed to be representative of the population as a whole, there were four modifiable risk factors that could be used to individually account for a significant proportion of cases of hyperuricemia. These risk factors were body mass index (BMI), the DASH diet, alcohol use, and diuretic use. Nevertheless, the corresponding serum urate variation that was explained by these risk variables was extremely tiny, which ironically hid their substantial prevalences. This provided real-life empirical evidence for the limits of this method in terms of evaluating common risk factors.

Wang, et al (2015)[13] conducted a study with 371 incident cases of gout (231 men and 140 women). Gout incidence rates per 1000 person-years were 6.82 (95% CI = 5.10-9.10) and 2.43 (2.18-2.71), respectively, for participants with and without

CKD. CKD was associated with gout in multivariable Cox models, with an HR of 1.88 (1.13-3.13) among men and 2.31 (1.25-4.24) among women. Additional analyses using different CKD definitions and a cross-sectional study yielded the same results. According to sensitivity analysis, the observed findings may be an underestimate of the true relative risk.

Other study showed the average SU drop was 48 mol/L, and at 24 months, it was 18 μmol/L, with no differences across diets (P > 0.05) after 6 months. During 6 months, body weight, HDL cholesterol (HDL-C), the ratio of total cholesterol to HDL-C, triglycerides, and insulin concentrations improved in all three groups (P <0.05). Controlling for confounders, changes in weight and fasting plasma insulin concentrations remained related to changes in SU (P <0.05). At 6 months, SU reductions for those with hyperuricemia were 113, 119, and 143 μmol/L for the low-fat, Mediterranean, and low-carbohydrate diets, respectively (all P for within-group comparison <0.001; P > 0.05 for between-group comparisons), and 65, 77, and 83 μmol/L, respectively, at 24 months (all P for within-group comparison < 0.01; P > 0.05 for between-group comparisons).[14]

Choi, et al (2020)[15] showed BMI, alcohol use, adherence to a DASH-style diet, and diuretic usage were all linked with serum urate levels and the existence of hyperuricemia. The corresponding proportional odds ratios (PARs) of hyperuricemia cases for overweight/obesity (prevalence 60%), nonadherence to a DASH-style diet (prevalence 82%), alcohol use (prevalence 48%), and diuretic use (prevalence 8%) were 44% (95% confidence interval [95% CI] 41%, 48%), 9% (95% CI 3%, 16%), 8% (95% CI 5%, 11%), When the exposure prevalence approached 100 percent, our simulation analysis revealed that the variance was approaching 0 percent.

DISCUSSION

Gout can be interpreted as arthritis due to increased levels of uric acid as a result of purine metabolism deposited in the form of monosodium urate crystals in the blood and joints. Normal uric acid levels in men and women differently. Normal uric acid levels in men range from 3.5–7 mg/dl and in women 2.6–6 mg/dl. An increase in uric acid levels up to 11 mg/dl has a high risk for the formation of kidney stones. The course of classic gout arthritis usually begins with an attack or someone has a history of having high uric acid checks above 7 mg/dl, and getting higher and higher over time. If so, the possibility of developing gout is even greater.[16,17]

Uric acid is a waste substance formed by the body when regenerating cells of people suffering from gout form more uric acid in the body and the body is not effective in removing uric acid through urine, so uric acid accumulates in the blood. Genetics, gender and nutrition (alcohol drinking, obesity) play an important role in the formation of gout. A high-purine diet can trigger gout attacks in people who have congenital abnormalities in purine metabolism resulting in increased uric acid production. A number of drugs can inhibit uric acid excretion by the kidneys. These include low-dose aspirin (<1-2/day), most diuretics, levopoda, diazoxide, nicotinic acid, acetazolamide, and ethambutol.[18]

Elevated serum uric acid levels can be caused by overproduction or decreased excretion of uric acid, or both. Uric acid is the end product of purine metabolism. Uric acid is a weak acid. The urate deposits in the joints are influenced by various factors, namely urate levels, cation concentrations, temperature, intra-articular dehydration and pH. These various factors contribute to the predilection for gout in the joint. Intra-articular dehydration and low temperature are predisposing factors for MSU crystallization. Purine synthesis involves two pathways, namely the de novo pathway and the salvage pathway. The de novo pathway involves the synthesis of purines and then uric acid via non-purine precursors. The initial substrate is ribose-5-phosphate, which is converted via a series of intermediates to purine nucleotides (inosinic acid, guanylic acid, adenylic acid). This pathway is controlled by a series of complex mechanisms, and there are several enzymes that accelerate the reaction, namely: 5-phosphoribosyl pyrophosphate (PRPP) synthetase and amido phosphoribosyl pyrophosphate (amido-PRT). There is a feedback inhibition mechanism by which purine nucleotides are formed, the function of which is to prevent over formation[18]

The study compared the results to those obtained from participants who had the lowest SU category. At the beginning of the research project, SU had a significant relationship with a number of risk factors and comorbidities, including hypertension, cardiovascular disease, and diabetes. Other risk factors included alcohol risk behavior (only in men), body mass index, estimated glomerular filtration rate, triglycerides, and triglyceride levels. These characteristics were shared by both sexes in the population.[17]

As a result of gender-related risk variables, researchers came to the conclusion that the proportion of males who suffer from gout is significantly higher than that of women. This is especially true for women who have not yet reached menopause. In this phase, estrogen's uricosuric action plays a significant part in the prevention of hyperuricemia, which is an important job for estrogen to perform. The conformance changes that take place in a person's connective tissue, especially their joints, become more pronounced as they get older. It is more simpler for MSU deposits to accumulate in the joints of elderly persons than it is in the joints of younger people.[6]

A prospective study based on 54 years of follow-up data from Framingham Heart Study (FHS) participants found that the risk of gout associated with CKD doubled (HR = 2.09; 95% CI 1.41 to 3.13) in participants without CKD or gout at baseline. These correlations maintained in both sexes, as well as in our supplementary analyses including individuals with CKD at baseline, and were independent of other well-known risk factors for gout, such as age, BMI, alcohol use, smoking,

hypertension, and diabetes. Overall, our findings provide prospective evidence that, regardless of other known risk factors, individuals with CKD have an elevated future risk of gout. Even when assuming excessive and improbable degrees of misclassification and bias, our sensitivity analysis revealed that the relative risk estimate is approximately 1.8, indicating that the true relative risk may be higher.[13]

Studies have avoided evaluating the effect of other potential predictors or controlling for them in favor of characterizing the risk for incident gout as a function of different degrees of SU. The temporal and causal relationships between a number of these parameters and SU are complex and, in some instances, possibly bidirectional, as with kidney function. This is a difficulty when attributing risk to individual factors/markers using conventional cohort analysis methodologies. Techniques such as Mendelian randomization based on genetic data may be more appropriate for this purpose.[19]

Dietary factors also contribute to the incidence of gout, especially in foods that contain lots of purines. Consumption of red meat such as beef and lamb can significantly increase MSU levels in the body. Seafood such as crustaceans also cause an increase in MSU, although not as high as red meat. Consumption of low-fat foods has been shown to reduce the likelihood of gout. the use of fructose sugar can increase MSU levels through the effect of GLUT9 which causes MSU reabsorption from the kidney tubules. The use of vitamin C has been shown to reduce MSU levels through uricosuric effects. The use of vitamin C at a dose of 500 mg/day for 2 months significantly reduced MSU levels up to 0.5 mg/dl.[16]

Other study showed all three diets led to similar improvements in SU and several cardiometabolic risk factors at both 6 and 24 months. This is important because it shows that patients who want to improve both their SU levels and their cardiometabolic health have more than one diet option. The choice can be based on the person's cardiometabolic comorbidity profiles. The person's personal preferences should also be taken into account to help increase adherence. So, an extra 4-year follow-up of the DIRECT study (so, a total of 6 years) showed that the Mediterranean diet might be the one that people stick to the most and lose weight the most steadily on.[14,20,21]

Obesity raises the risk of gout by elevating serum urate levels, both by reducing renal urate excretion and by increasing urate synthesis. Obesity is causally related with serum urate levels in the general population, according to Mendelian randomization studies; weight loss by bariatric surgery or lifestyle modification reduces serum urate. Regarding food and alcohol, earlier metabolic loading tests with purine, fructose, and alcohol verified their serum urate-raising impact, whereas dairy products demonstrated serum urate-lowering effects in three experimental investigations, including two randomized trials.[15]

Gout patients should avoid foods and drinks that can increase serum uric acid levels. These include red meat, organ meats, seafood, fermented foods, alcohol, and foods and drinks sweetened with high-fructose corn syrup. The patient also drinks lots of water. This is done to minimize uric acid precipitation in the urine and prevent uric acid type kidney stones from occurring. Suggested activities in patients with gout include routine and regular aerobic activity. Moderate light physical activity is recommended, for example walking, 150 minutes per week or 30 minutes per day to maintain body weight. Patients should avoid physical activities that increase the risk of trauma to the joints. Patients should as much as possible avoid drugs that can increase blood uric acid. Examples are diuretics such as hydrochlorothiazide, aspirin, and cyclosporine.[22–24]

CONCLUSION

According to research, there are a number of characteristics that increase a person's likelihood of developing gout. They include drinking to excess (only in men), having a high body mass index, having a low estimated glomerular filtration rate, and having high triglyceride levels. Gout sufferers should avoid uric acid-raising meals and beverages. The patient drinks plenty of water. Gout sufferers should exercise regularly. To maintain weight, walk 150 minutes per week or 30 minutes each day. Avoid uric acid-raising medications like hydrochlorothiazide, aspirin, and cyclosporine.

REFERENCE

[1] Firestein GS, Budd RC, Harris ED, McInnes IB, Ruddy S, Sergent JS. KELLEY ' S Textbook of Rheumatology. Goldring MB, editor. philadelphia; 2009 p. 37–60.
[2] Ragab G, Elshahaly M, Bardin T. Gout: An old disease in new perspective–A review. J Adv Res. 2017;8(5):495–511.
[3] Neogi T. Gout. Ann Intern Med. 2016 Jul;165(1):ITC1–16.
[4] Fauci AS, Jameson JL, Kasper D, et al. Harrison's Principles of Internal Medicine 19th Edition. New York: McGraw-Hill Education; 2018.
[5] Dalbeth N, Merriman TR, Stamp LK. Gout. Lancet (London, England). 2016 Oct;388(10055):2039–52.
[6] Singh JA, Gaffo A. Gout epidemiology and comorbidities. In: Seminars in arthritis and rheumatism. Elsevier; 2020. p. S11–6.
[7] Dehlin M, Jacobsson L, Roddy E. Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors. Nat Rev Rheumatol. 2020;16(7):380–90.
[8] Kuo C-F, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: prevalence, incidence and risk factors. Nat Rev Rheumatol. 2015;11(11):649–62.
[9] Clebak KT, Morrison A, Croad JR. Gout: Rapid evidence review. Am Fam Physician. 2020;102(9):533–8.

[10] Johnson RJ. Why focus on uric acid? Curr Med Res Opin. 2015;31 Suppl 2:3–7.
[11] Roddy E, Doherty M. Epidemiology of gout. Arthritis Res Ther. 2010;12(6):223.
[12] Wilson L, Saseen JJ. Gouty arthritis: a review of acute management and prevention. Pharmacother J Hum Pharmacol Drug Ther. 2016;36(8):906–22.
[13] Wang W, Bhole VM, Krishnan E. Chronic kidney disease as a risk factor for incident gout among men and women: retrospective cohort study using data from the Framingham Heart Study. BMJ Open. 2015;5(4):e006843.
[14] Yokose C, McCormick N, Rai SK, Lu N, Curhan G, Schwarzfuchs D, et al. Effects of low-fat, Mediterranean, or low-carbohydrate weight loss diets on serum urate and cardiometabolic risk factors: a secondary analysis of the dietary intervention randomized controlled trial (DIRECT). Diabetes Care. 2020;43(11):2812–20.
[15] Choi HK, McCormick N, Lu N, Rai SK, Yokose C, Zhang Y. Population impact attributable to modifiable risk factors for hyperuricemia. Arthritis Rheumatol. 2020;72(1):157–65.
[16] Dalbeth N, Gosling AL, Gaffo A, Abhishek A. Gout. Lancet (London, England). 2021 May;397(10287):1843–55.
[17] Kapetanovic MC, Nilsson P, Turesson C, Englund M, Dalbeth N, Jacobsson L. The risk of clinically diagnosed gout by serum urate levels: results from 30 years follow-up of the Malmö Preventive Project cohort in southern Sweden. Arthritis Res Ther. 2018;20:1–10.
[18] Bardin T. Chapter 4 - Tophi: Clinical and Biological Features. In: Schlesinger N, Lipsky PEBT-G, editors. Elsevier; 2019. p. 37–46. Available from: https://www.sciencedirect.com/science/article/pii/B978032354823600004X
[19] Zheng J, Baird D, Borges M-C, Bowden J, Hemani G, Haycock P, et al. Recent developments in Mendelian randomization studies. Curr Epidemiol reports. 2017;4:330–45.
[20] Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, Greenberg I, et al. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N Engl J Med. 2008;359(3):229–41.
[21] Schwarzfuchs D, Golan R, Shai I. Four-year follow-up after two-year dietary interventions. N Engl J Med. 2012;367(14):1373–4.
[22] FitzGerald JD, Dalbeth N, Mikuls T, Brignardello-Petersen R, Guyatt G, Abeles AM, et al. 2020 American College of Rheumatology guideline for the management of gout. Arthritis Care Res (Hoboken). 2020;72(6):744–60.
[23] Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Am Coll Rheumatol. 2020;72(2):220–33.
[24] Lorenzo JPP, Sollano MHMZ, Salido EO, Li-Yu J, Tankeh-Torres SA, Wulansari Manuaba IAR, et al. 2021 Asia-Pacific League of Associations for Rheumatology clinical practice guideline for treatment of gout. Int J Rheum Dis. 2022;25(1):7–20.