Perspectives on the Epidemiology of Gout and Hyperuricemia

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Abstract

Gout is the most common inflammatory arthritic condition affecting more men than women. Hyperuricemia and the deposition of urate crystals into the joints are the hallmarks of gout. The prevalence of gout and hyperuricemia is rising in the United States and world-wide possibly due to the aging population, comorbidities, and other lifestyle factors. Gout and serum uric acid (SUA) levels are highly heritable, underscoring the role of genetics on disease risk and possibly the racial disparities in gout prevalence. However, high consumption of high fructose corn syrup, alcohol, select dietary lifestyles, and use of diuretics are associated with higher SUA levels and increased risk for developing gout. Adopting healthy diet and lifestyle modifications can lower SUA levels. Nonetheless, diet-based approaches for the management of gout should remain a secondary approach to urate lowering therapy.

Epidemiology of Gout and Hyperuricemia

Gout is the most common inflammatory arthritic condition characterized by the deposition of urate crystals into the joints.[1] Data from major US healthcare systems and the National Health and Nutrition Examination Survey (NHANES) have shown a rise in prevalence of gout and hyperuricemia (Figure 1).[2,3] In the United States, the prevalence of gout has significantly increased from 2.9% in NHANES III 1988-1994 to 3.9% in NHANES 2007-2008.[2] The worldwide prevalence and incidence of gout are also rising. For instance, the South Korean National Health claims indicated that the prevalence increased from 0.35% in 2007 to 0.75% in 2015, and the incidence rate significantly increased from 1.5 in 2007 to 1.9 in 2015 per 1000 per year.[4] Conversely, the prevalence of gout remains unchanged in some countries. A study in Taiwan reported that the prevalence of gout remained relatively unchanged from 6.4% in 2005 to 6.2% in 2010.[5]

The prevalence of gout substantially differs across geographical regions of the world. While Greece presents with the highest prevalence in Europe (4.75%), other countries like the Philippines, Jamaica, Iran, South Korea, and select African countries have reported prevalence of less than 1%.[4,6] This geographical differential in prevalence further supports the role of environment, dietary habits, and other lifestyle behaviors that modulate the risk for developing gout.[7]

In the United States, the prevalence of hyperuricemia has significantly increased from 19.1% in NHANES 1988-1994 to 21.5% in NHANES 2007-2008.[2] Although the prevalence of gout is markedly different between men (6%) and women (2%), the prevalence of hyperuricemia is similar between men (21.2%) and women (21.6%).[2] This considers the gender difference in the case definition of hyperuricemia (SUA >5.7 mg/dL for women vs >6.8 mg/dL for men). According to the NHANES 2007-2008, the mean serum uric acid (SUA) level was 6.14mg/dL among men and 4.87mg/dL among women.

The different thresholds for classifying hyperuricemia and prevalence of gout between men and women have a variety of sources such as amount of alcohol consumption and muscle mass.[8] In addition, circulating estrogen levels significantly affects the risk of hyperuricemia and gout between sexes due to its uricosuric effect.[9,10] However, this protective effect decreases as women reach the postmenopausal age when circulating estrogen levels decline. Additionally, as age increases the risks of developing hyperuricemia and gout also increase due to declining kidney function, risk of dehydration, and polypharmacy due to the multiple comorbidities.[3] Thus, the combination of decreased estrogen levels and complications of aging-related comorbidities suggest that women might be at a higher risk for developing gout at later stages in life than men.

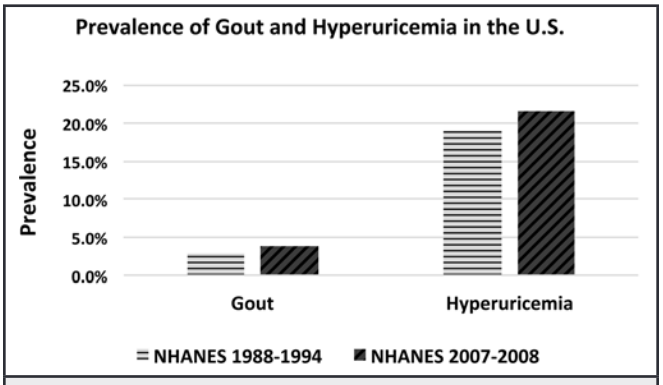

Figure 1. Changes in the Prevalence of Gout and Hyperuricemia in United States

There are multiple limitations associated with the methods used to assess the prevalence or incidence of gout such as relying on participants' self-report, recall bias, sampling limitations, misdiagnosis or case-definition of gout, and the timing of conducting the study. Therefore, the need for replication and longitudinal studies are warranted to accurately quantify the prevalence and incidence of gout, which is a debilitating and costly disease to its sufferers and society at large.[11]

Hyperuricemia and Gout in Hawai'i

Epidemiological studies have found disparities in the ethnocultural and geographical distribution of hyperuricemia and gout in the Asian-Pacific regions.[12,13] These findings have led investigators to postulate that indigenous groups throughout the Oceania regions may be predisposed to hyperuricemia and gout. The state of Hawai'i has the largest Native Hawaiian and Other Pacific Islander (NHOPI) populations in the United States.[14] The prevalence of hyperuricemia and gout in NHOPI living in Hawai'i is a knowledge gap.[12] Without data on the distribution of hyperuricemia and gout burden, it is not possible to directly ascertain the impact of both conditions in Hawai'i, reduce their prevalence, and mitigate their consequences, such as diabetes and chronic kidney disease (CKD).[12,15,16] Moreover, individuals of Pacific Islander descent living in Hawai'i are at an increased risk for developing hyperuricemia and gout, partly due to possible genetic predisposition and historical change in dietary lifestyles.[12]

While there is an expectation of a high prevalence of hyperuricemia and gout in Hawai'i, there is no comprehensive assessment of this prevalence reported in the literature.[12] Additionally, the hyperuricemia and gout prevalence reports from Hawai'i are either significantly outdated or lacking for select ethno-racial groups such as the NHOPI.[17] The absence of this data is a prime example of health disparity of knowledge in these unique populations and missed opportunities to address their high risk for developing CKD and other gout-related comorbidities.

Pathogenesis of Hyperuricemia and Gout

Purines are converted to hypoxanthine, xanthine, and ultimately uric acid (UA) via the xanthine oxidase enzyme. Based on an average purine content diet, 800-1000mg of UA is produced daily.[18] Of this amount, 500-600mg is produced endogenously while the remaining 200-300mg is produced from dietary sources of purines.[18] Of the amount produced daily, approximately 70% is excreted by the kidney while the remainder is eliminated via the gastrointestinal tract, where it is degraded by bacterial uricase (Figure 2).[1]

While kidney function is critical in UA disposition, the role of uricase-producing bacteria in the intestine raises the question of whether changes in gut microbiome influences the risk of developing gout. A small study of gout patients compared to those with type 2 diabetes and metabolic syndrome identified that the intestinal microbiota profiles are distinct in both the organismal and functional structures. Furthermore, the reference microbial gene catalogue for gout cases revealed disorders associated with purine metabolism and butyric acid biosynthesis, both of which to be the basis for developing gout.[19]

The level of SUA is the net effect of dietary intake of purine sources, endogenous cell turnover, and UA excretion. The imbalance between UA production and excretion is the hallmark of hyperuricemia and progenitor for monosodium urate crystal formation. Defective renal elimination of UA, known as UA underexcreters, accounts for 80%-90% of gout cases. However, inherited genetic disorders such as Lysch Nyhan Syndrome, Tumor Lysis Syndrome, or high intake of purine sources can result in UA overproduction, which accounts for 10% of gout subtypes.[1,18,20,21]

UA is extensively (~90%) reabsorbed from the kidney via the Four Compartment Theory, which allows a small fraction of UA to be excreted (Figure 3).[22] Though SUA levels are inversely associated with kidney function, higher baseline SUA levels can naturally exist in normal kidney function. The etiology of such discordance between kidney function and SUA levels in some individuals has been attributed to genetic variants within select UA transporters, mainly ABCG2, NPT1, and URAT1, which can significantly modulate SUA levels.[23] These genetic variants can render some individuals to be more efficient at reabsorbing UA while making others less efficient at excreting UA (Figure 2).

Genetics of Hyperuricemia and Gout

Hyperuricemia and gout are highly heritable with estimates of up to 45% and 65%, respectively.[24] The recent advances in genetic tools applied to large populations, such as genome-wide association studies (GWAS), have helped to elucidate major genetic variants in the UA disposition pathway which may predict hyperuricemia or gout. The genes that have been repeatedly identified to be associated with SUA levels mainly involve transporter-encoding genes affecting UA excretion such as *ABCG2* and *SLC17A1*, UA reabsorption genes such as *SLC2A9*, *SLC22A11* and *SLC22A12*, the lipid-metabolizing gene *GCKR*, and the scaffolding gene *PDZK1*.[25]

The prevalence of hyperuricemia and gout varies with race and ethnicity.[26] For example, African-Americans and Hmong tend to have a higher prevalence of gout compared to Caucasians and Europeans.[2,26,27] This difference in racial prevalence parallels the prevalence of genetic variants, primarily the single nucleotide polymorphisms consistent with those identified by GWAS.[23,28-30] These genetic findings may play a role in the explanation for why some populations have higher documented prevalence of gout.[6,31]

Although these genetic variants are found to be differentially prevalent across racial groups, at least one group studying several populations found that the magnitude and direction of impact these genetic variants were consistent across most of the studied populations.[29] The etiology of gout is a heterogeneous process involving genetic and non-genetic factors. While key genetic variants associated with gout have been identified, recent candidate genes studies and GWAS in Japanese patients with

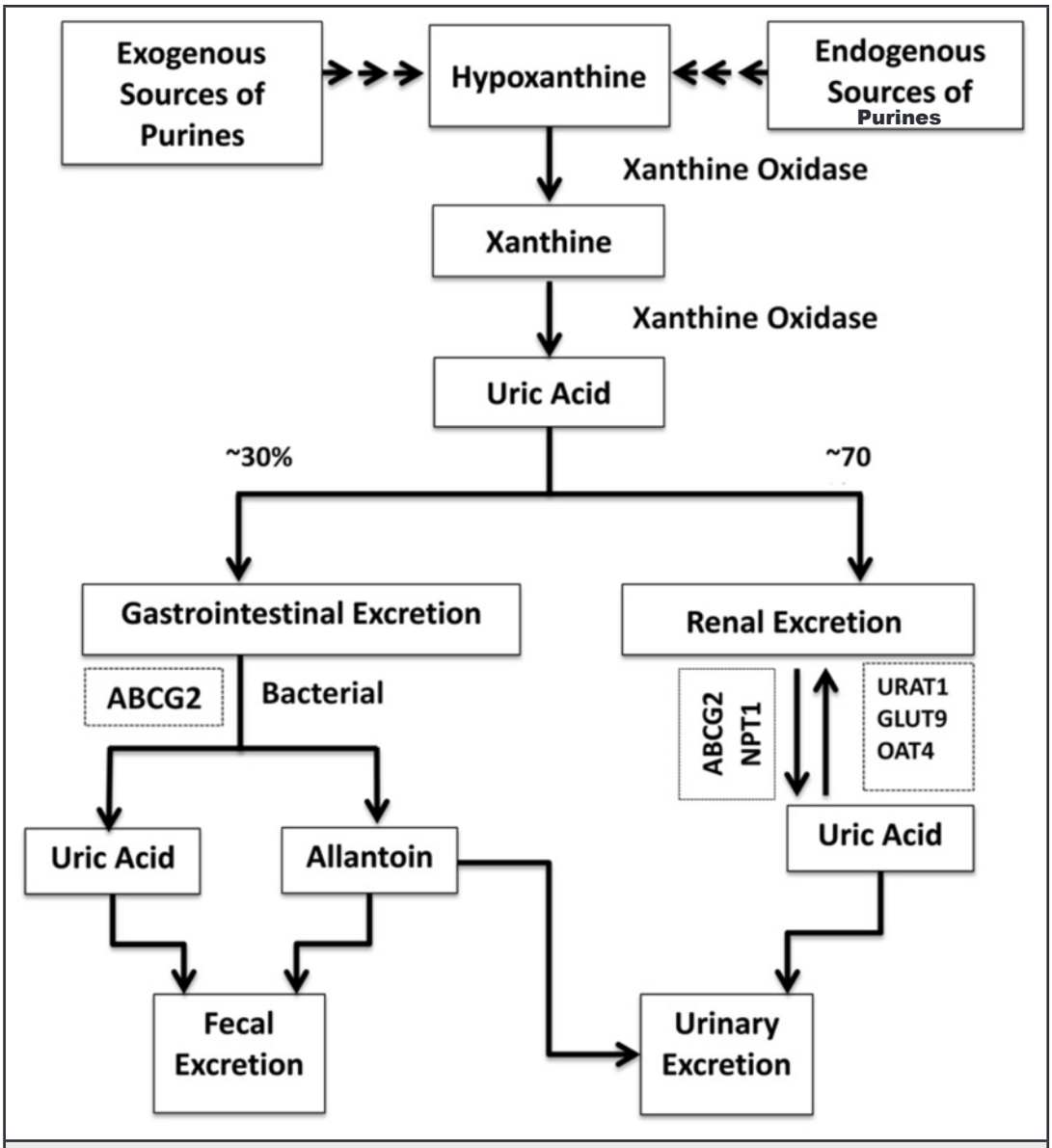

Figure 2. Purine Metabolism and Disposition of Uric Acid

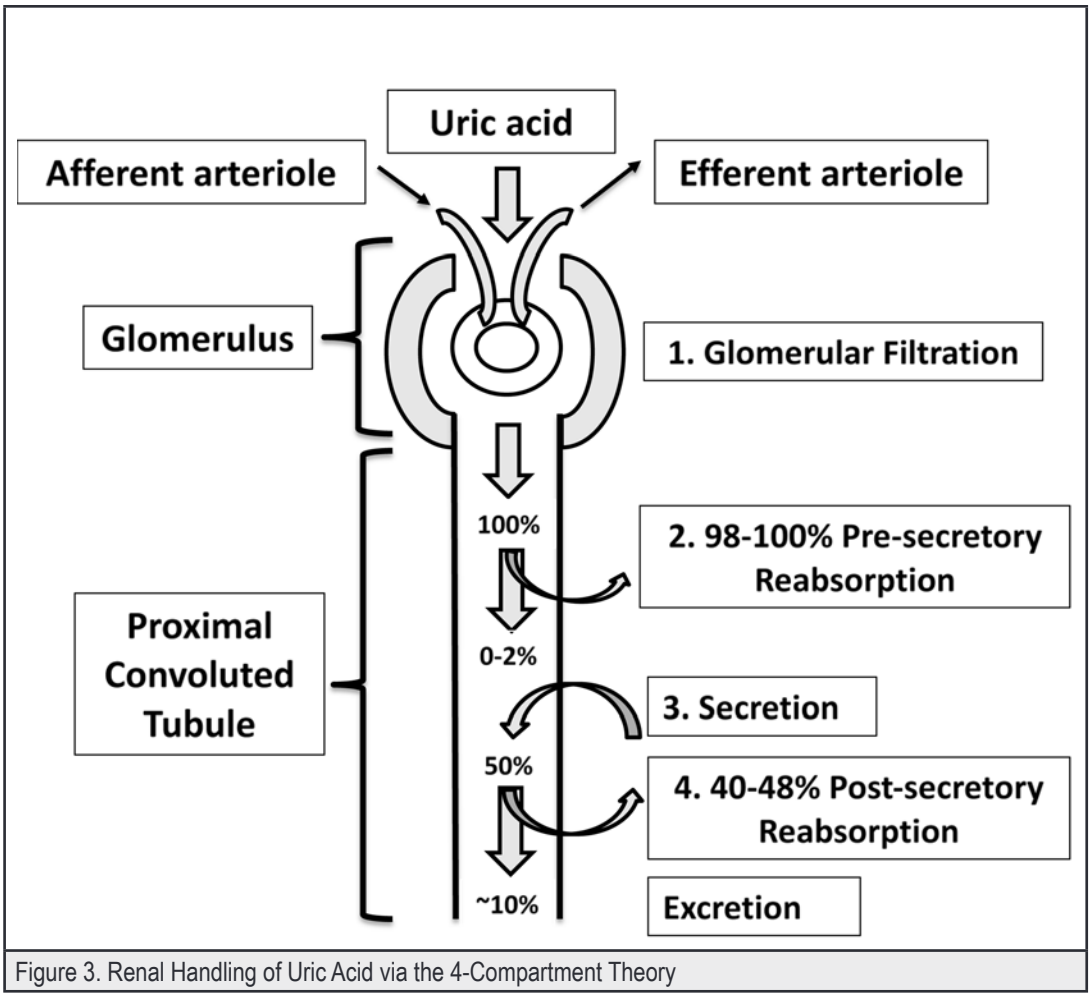

Figure 3. Renal Handling of Uric Acid via the 4-Compartment Theory

gout have suggested some genetic variants are associated with the gout subtypes overproduction, underexcretion, or combined.[32] Specifically, genetic variants were found in *SLC16A9* and *SLC22A11*, which may predict the overproduction and underexcretion of UA phenotype, respectively.[33,34] Comparably, genetic polymorphisms within the efflux *ABCG2* transporter were found to influence the response to urate lowering therapy, mainly allopurinol.[35,36]

Hyperuricemia and Gout Risk Factors

Though age is a key predictor of developing gout, male sex is associated with higher incidence of gout than females (3:1).[3] However, postmenopausal women have a similar or increased risk for developing gout compared to men due to declining estrogen levels. In men, testosterone replacement therapy is associated with elevated SUA levels and increased blood pressure through the activation of the renin-angiotensin system (RAAS).[37,38] This observation is consistent with the potential effect of hyperuricemia on the development of hypertension though the activation of RAAS.[39] Comorbidities, use of select drugs, and sex hormone levels all modulate SUA and thus the risk of gout. Specifically, the changes in androgen levels in aging men and circulating estrogen in postmenopausal women underscore the comparable risk of developing gout in both elderly men and women.

Diuretics Use and Gout

Diuretics are also associated with elevated SUA and significantly increase the risk of worsening gout symptoms and new onset of gout flares.[40] An analysis of a large population-based cohort identified that the use of thiazide or loop diuretics was significantly associated with new incidence of gout compared to no use of diuretics (HR 1.48 [95%CI, 1.11 to 1.98]). Although not significantly different, the loop diuretics had a higher risk (HR 2.31 [95% CI, 1.36 to 3.91]) than thiazide diuretics (HR 1.44 [95% CI, 1.00 to 2.10]) with incident gout.[41]

Effect of Select Diet on Uric Acid and Gout

High Fructose Corn Syrup

It is well documented that higher intake of purine sources, especially red meat and seafood, can worsen existing gout symptoms or increase risk of developing gout. Higher intake of high fructose corn syrup sources in products such as soft drinks can also result in new onset of acute gout attacks.[42,43] The con-

sumption of high fructose corn syrup has dramatically increased over the past few decades which has been cited as a contributing factor for the increase in the prevalence of hyperuricemia and gout in countries where fructose is commercially used as a sweetener.[44] The mechanism by which fructose increases SUA is not clearly understood, but it has been proposed that fructose gets reabsorbed from the kidney and further metabolized to fructose 1-phosphate in the liver.[45] This conversion results in a sharp depletion of ATP subsequently increasing UA levels. The depletion of ATP further stimulates the synthesis of purine nucleotides causing more UA production.[42] In addition, a substantial amount of ingested fructose is converted into lactate, which competes with UA for excretion causing an increase in SUA levels.[46-48] Collectively, these are the mechanisms by which consumption of high fructose corn syrup can increase the risk of developing gout or gout attacks.[43]

Alcohol

Select forms of alcohol have also been implicated in the development of gout or gout attacks, mainly due to the varying levels of purine contents. Specifically, beer tends to have the greatest effect on UA due to high purine contents and high percent of alcohol, while wine shows the lowest risk.[8,49] The effect of alcohol on UA production results from the conversion of ethanol into Acetyl-CoA, which leads to degradation of purine trinucleotides which increases levels of UA precursors. Like fructose, the formation of lactic acid from ethanol metabolism further leads to higher SUA.

Diet and Urine pH

UA is a weak acid with a pKa of 5.8 and predominantly found in the ionized form, urate. Since urine pH is critical for determining the amount of UA that is reabsorbed from the proximal convoluted tubule (PCT), we can postulate that chronic exposure to pH modifiers have a substantive effect on the amount of ionized form of urate in the PCT.[50] Thus, sources that acidify the urine may enhance the UA reabsorption, causing the buildup of UA in the kidney and resulting in an acute UA nephropathy and possible UA kidney stones.[7,51] On the contrary, diets rich in reduced fat such as skimmed milk have been shown to decrease UA absorption.[7]

Diet and Gout Triggers

Flynn, et al, surveyed the frequency of select dietary gout attack triggers in 2051 New Zealander patients with gout.[52] The study identified that 71% of the study participants self-reported one or more dietary triggers of gout attack. The most commonly reported triggers were seafood (63%), alcohol (47%), red meat (35%), and tomatoes (20%).[52] While the effect of seafood, alcohol and red meat on the risk of gout is well documented, the role of tomatoes in gout attacks is startling. Although the study did not demonstrate the effect of tomato consumptions on acute gout attacks, it explored the physiological basis for this observation by associating the weekly consumption of tomatoes and SUA levels. In fact, retrospective analyses of major longitudinal cohorts such as the Cardiovascular Health Study and the Framingham Heart Study showed a significant increase in SUA levels of 0.7 μmo/L (0.012 mg/dL) with one serving per week in tomato consumption.[52] On one hand, the study corroborates that the avoidance of tomato consumption in patients with gout is not unfounded practice. On the other hand, a prospective clinical trial in 35 young women showed that pre-meal tomato intake has been significantly associated with a decrease in SUA with 0.16 mg/dL.[53] This difference in outcomes can be attributed to the method of tomato preparation, which can influence the contents of chemicals that can affect urate levels.

Diet Prescription for Gout

Weight loss, physical exercise, vitamin C supplementation, soy-containing products, low-fat milk, DASH diet, and consumption of coffee and cherries have been linked to lowering SUA and reduced incidence of acute gout attacks.[7,54-58] Counseling patients on the importance of dietary and lifestyle modifications and avoidance of gout attack triggers can garner additional benefits for optimal management of gout. However, given the current evidence, the excessive focus on the dietary aspect of gout management may adversely and negatively affect the adherence to the urate-lowering therapy in patients with gout. Thus, dietary intervention should be a secondary approach to urate-lowering therapy to manage patients with gout while reinforcing gout pharmacotherapy as the focal point in gout management.

Conclusions and Clinical Implications

The rise in prevalence of gout could be related to trends such as aging, comorbidities, polypharmacy, and select lifestyle factors. Gout is associated with reduced quality of life and high care cost. The development of gout and hyperuricemia is a heterogeneous process that involves multiples factors including genetics, drugs, and diet. These factors can be exploited as tools to assess the patient's risk for developing hyperuricemia and gout as well as opportunities to mitigate the risk of gout attacks and drug selection.

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References

1. Choi HK, Mount DB, Reginato AM, American College of P, American Physiological S. Pathogenesis of gout. *Ann Intern Med.* 2005;143(7):499-516.
2. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. *Arthritis and Rheumatism.* 2011;63(10):3136-3141.
3. Wallace KL, Riedel AA, Joseph-Ridge N, Wortmann R. Increasing prevalence of gout and hyperuricemia over 10 years among older adults in a managed care population. *The Journal of Rheumatology.* 2004;31(8):1582-1587.
4. Kim JW, Kwak SG, Lee H, Kim SK, Choe JY, Park SH. Prevalence and incidence of gout in Korea: data from the national health claims database 2007-2015. *Rheumatology International.* 2017;37(9):1499-1506.
5. Kuo CF, Grainge MJ, See LC, et al. Epidemiology and management of gout in Taiwan: a nationwide population study. *Arthritis Research & Therapy.* 2015;17:13.
6. Kuo CF, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: prevalence, incidence and risk factors. *Nat Rev Rheumatol.* 2015;11(11):649-662.
7. Hyon K. Choi M, DrPH. A prescription for lifestyle change in patients with hyperuricemia and gout. *Current Opinion in Rheumatology.* 2010.
8. Hyon K Choi KA, Elizabeth W Karlson, Walter Willett, Gary Curhan. Alcohol intake and risk of incident gout in men: a prospective study. *Lancet.* 2004;363:1277–1281.
9. Adamopoulos D, Vlassopoulos C, Seitanides B, Contoyiannis P, Vassilopoulos P. The relationship of sex steroids to uric acid levels in plasma and urine. *Acta Endocrinologica.* 1977;85(1):198-208.
10. Takiue Y, Hosoyamada M, Kimura M, Saito H. The effect of female hormones upon urate transport systems in the moust kidney. *Nucleosides Nucloetides Nucleic Acids.* Feb 2011;30(2):113-119.
11. Brook RA, Kleinman NL, Patel PA, et al. The economic burden of gout on an employed population. *Current Medical Research and Opinion.* 2006;22(7):1381-1389.
12. Thompson MD. Insights in Public Health: Hyperuricemia and Gout in Hawai'i. *Hawaii J Med Public Health.* 2018;77(5):121-124.
13. R Buckley H. Epidemiology of gout: Perspectives from the past. *Current Rheumatology Reviews.* 2011;7(2):106-113.
14. Hixson LK, Hepler BB, Kim MO. *The native Hawaiian and other Pacific Islander population: 2010.* US Department of Commerce, Economics and Statistics Administration, US. 2012.
15. Aluli NE, Jones KL, Reyes PW, Brady SK, Tsark JU, Howard BV. Diabetes and cardiovascular risk factors in Native Hawaiians. *Hawaii Med J.* 2009;68(7):152-157.
16. Mau MK, West MR, Shara NM, et al. Epidemiologic and clinical factors associated with chronic kidney disease among Asian Americans and Native Hawaiians. *Ethnicity and Health.* 2007;12(2):111-127.
17. Yano K, Rhoads G, Kagan A. Epidemiology of serum uric acid among 8000 Japanese-American men in Hawai'i. *J Chronic Dis.* 1977;30(3):171-184.
18. Lloyd A, Burchett I. Broadsheet number 43: The role of the laboratory in the investigation and management of hyperuricemia. *Pathology.* 1998;30(2):141-146.
19. Guo Z, Zhang J, Wang Z, et al. Intestinal Microbiota Distinguish Gout Patients from Healthy Humans. *Sci Rep.* 2016;6:20602.
20. Lang F, Greger R, Oberleithner H, et al. Renal handling of urate in healthy man in hyperuricaemia and renal insufficiency: circadian fluctuation, effect of water diuresis and of uricosuric agents. *Eur J Clin Invest.* 1980;10(4):285-292.
21. Marangella M. Uric acid elimination in the urine. Pathophysiological implications. C*ontrib Nephrol.* 2005;147:132-148.
22. Koopman WJ. *Arthritis and Allied Conditions: A Textbook of Rheumatology.* Lippincott Williams & Wilkins; 2001
23. Kolz M, Johnson T, Sanna S, et al. Meta-analysis of 28,141 individuals identifies common variants within five new loci that influence uric acid concentrations. *PLoS Genet.* 2009;5(6):e1000504.
24. Voruganti VS, Laston S, Haack K, et al. Serum uric acid concentrations and SLC2A9 genetic variation in Hispanic children: the Viva La Familia Study. *Am J Clin Nutr.* 2015;101(4):725-732.
25. Yang QO, Kottgen A, Dehghan A, et al. Multiple Genetic Loci Influence Serum Urate Levels and Their Relationship With Gout and Cardiovascular Disease Risk Factors. *Circ-Cardiovasc Gene.* 2010;3(6):523-530.
26. Singh JA. Racial and gender disparities among patients with gout. *Current Rheumatology Reports.* 2013;15(2):307.
27. Portis AJ, Laliberte M, Tatman P, et al. High prevalence of gouty arthritis among the Hmong population in Minnesota. *Arthritis Care & Research.* Oct 2010;62(10):1386-1391.
28. Roman YM, Culhane-Pera KA, Menk J, Straka RJ. Assessment of genetic polymorphisms associated with hyperuricemia or gout in the Hmong. *Personalized Medicine.* 2016;13(5): 9-440.
29. Kottgen A, Albrecht E, Teumer A, et al. Genome-wide association analyses identify 18 new loci associated with serum urate concentrations. *Nature Genetics.* 2013;45(2):145-154.
30. Charles BA, Shriner D, Doumatey A, et al. A genome-wide association study of serum uric acid in African Americans. *BMC Medical Genomics.* 2011;4:17.
31. Klemp P, Stansfield SA, Castle B, Robertson MC. Gout is on the increase in New Zealand. *Ann Rheum Dis.* 1997;56(1):22-26.
32. Matsuo H, Yamamoto K, Nakaoka H, et al. Genome-wide association study of clinically defined gout identifies multiple risk loci and its association with clinical subtypes. *Ann Rheum Dis.* 2016;75(4):652-659.
33. Nakayama A, Matsuo H, Shimizu T, et al. Common missense variant of monocarboxylate transporter 9 (MCT9/SLC16A9) gene is associated with renal overload gout, but not with all gout susceptibility. *Hum Cell.* 2013;26(4):133-136.
34. Sakiyama M, Matsuo H, Shimizu S, et al. A common variant of organic anion transporter 4 (OAT4/SLC22A11) gene is associated with renal underexcretion type gout. *Drug Metab Pharmacokinet.* 2014;29(2):208-210.
35. Wen CC, Yee SW, Liang X, et al. Genome-wide association study identifies ABCG2 (BCRP) as an allopurinol transporter and a determinant of drug response. *Clinical Pharmacology and Therapeutics.* 2015;97(5):518-525.
36. Roberts RL, Wallace MC, Phipps-Green AJ, et al. ABCG2 loss-of-function polymorphism predicts poor response to allopurinol in patients with gout. *The pharmacogenomics Journal.* 2016.
37. Huisman HW, Schutte AE, Van Rooyen JM, et al. The influence of testosterone on blood pressure and risk factors for cardiovascular disease in a black South African population. *Ethn Dis.* Summer 2006;16(3):693-698.
38. Kurahashi H, Watanabe M, Sugimoto M, et al. Testosterone replacement elevates the serum uric acid levels in patients with female to male gender identity disorder. *Endocr J.* 2013;60(12):1321-1327.
39. Feig DI. Hyperuricemia and hypertension. *Advances in Chronic Kidney Disease.* 2012;19(6):377-385.
40. Choi HK, Soriano LC, Zhang Y, Rodriguez LA. Antihypertensive drugs and risk of incident gout among patients with hypertension: population based case-control study. *BMJ.* 2012;344:d8190.
41. McAdams DeMarco MA, Maynard JW, Baer AN, et al. Diuretic use, increased serum urate levels, and risk of incident gout in a population-based study of adults with hypertension: the Atherosclerosis Risk in Communities cohort study. *Arthritis and Rheumatism.* 2012;64(1):121-129.
42. Johnson RJ, Nakagawa T, Sanchez-Lozada LG, et al. Sugar, uric Acid, and the etiology of diabetes and obesity. *Diabetes.* 2013;62(10):3307-3315.
43. Hyon K Choi, Gary Curhan. Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. *BMJ.* 2008.
44. Rho YH, Zhu Y, Choi HK. The epidemiology of uric acid and fructose. *Seminars in Nephrology.* 2011;31(5):410-419.
45. Batt C, Phipps-Green AJ, Black MA, et al. Sugar-sweetened beverage consumption: a risk factor for prevalent gout with SLC2A9 genotype-specific effects on serum urate and risk of gout. *Ann Rheum Dis.* Sep 11 2013.
46. Lecoultre V, Egli L, Theytaz F, Despland C, Schneiter P, Tappy L. Fructose-induced hyperuricemia is associated with a decreased renal uric acid excretion in humans. *Diabetes Care.* 2013;36(9):e149-150.
47. Mayes PA. Intermediary metabolism of fructose. *Am J Clin Nutr.* 1993;58:745S-765S.
48. Okada Y, Sim X, Go MJ, et al. Meta-analysis identifies multiple loci associated with kidney function-related traits in east Asian populations. *Nature Genetics.* 2012;44(8):904-909.
49. Wang M, Jiang X, Wu W, Zhang D. A meta-analysis of alcohol consumption and the risk of gout. *Clin Rheumatol.* 2013;32(11):1641-1648.
50. Barr WG. Uric Acid. In: rd, Walker HK, Hall WD, Hurst JW, eds. *Clinical Methods: The History, Physical, and Laboratory Examinations.* Boston1990.
51. Tsai YT, Liu JP, Tu YK, et al. Relationship between dietary patterns and serum uric acid concentrations among ethnic Chinese adults in Taiwan. *Asia Pac J Clin Nutr.* 2012;21(2):263-270.
52. Flynn TJ, Cadzow M, Dalbeth N, et al. Positive association of tomato consumption with serum urate: support for tomato consumption as an anecdotal trigger of gout flares. *BMC Musculoskeletal Disorders.* 2015;16(1):196.
53. Vinha AF, Barreira SV, Costa AS, Alves RC, Oliveira MBP. Pre-meal tomato (Lycopersicon esculentum) intake can have anti-obesity effects in young women? *International Journal of Food Sciences and Nutrition.* 2014;65(8):1019-1026.
54. Juraschek SP, Gelber AC, Choi HK, Appel LJ, Miller ER. Effects of the Dietary Approaches to Stop Hypertension (DASH) diet an dsodium intake on serum uric acid. *Arthritis & Rheumatology.* 2016;68(12):3002-2009.
55. Zhang Y, Neogi T, Chen C, Chaisson C, Hunter DJ, Choi HK. Cherry consumption and decreased risk of recurrent gout attacks. *Arthritis and Rheumatism.* 2012;64(12):4004-4011.
56. Teng GG, Pan A, Yuan JM, Koh WP. Food Sources of Protein and Risk of Incident Gout in the Singapore Chinese Health Study. *Arthritis Rheumatol.* 2015;67(7):1933-1942.
57. Bae J, Shin DH, Chun BY, et al. The effect of vitamin C intake on the risk of hyperuricemia and serum uric acid level in Korean Multi-Rural Communities Cohort. *Joint, Bone, Spine: Revue du Rhumatisme.* 2014;81(6):513-519.
58. Liu ZM, Ho CS, Chen YM, Woo J. Can soy intake affect serum uric acid level? Pooled analysis from two 6-month randomized controlled trials among Chinese postmenopausal women with prediabetes or prehypertension. *Eur J Nutr.* 2015;54(1):51-58.