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The Epidemiology of Uric Acid and Fructose

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Abstract

During the past few decades, the mean serum uric acid levels and the prevalence of hyperuricemia in the general population appear to have increased. Correspondingly, the prevalence and incidence of gout have doubled. Potential reasons behind these trends include the increasing prevalence of obesity and metabolic syndrome, western life-style factors, increased prevalence of medical conditions (e.g. renal conditions, hypertension, and cardiovascular disorders) and use of medications that increase uric acid levels (e.g. diuretics and low-dose aspirin). The substantial increase in sugar-sweetened soft drinks and associated fructose consumption has also coincided with the secular trend of hyperuricemia and gout. Recently, several large-scale epidemiologic studies have clarified a number of these long-suspected risk factors in relation with hyperuricemia and gout. Furthermore, recent studies have illuminated the substantial comorbidities of hyperuricemia and gout, particularly metabolic-cardiovascular-renal conditions. While many prospective studies have suggested an independent association between serum uric acid levels and the future risk of cardiovascular-metabolic morbidities and mortality, only a limited number of randomized clinical trials and observational studies have recently demonstrated that the use of allopurinol can be beneficial against these outcomes. As these data are scarce and the effects of allopurinol might not be limited to lowering serum uric acid levels, the potential causal role of uric acid on these outcomes remains to be clarified with further studies.

Keywords: Uric Acid, Hyperuricemia, Gout, Epidemiology, Cardiovascular Risk

Introduction

Hyperuricemia is the precursor of gout, which is the most common inflammatory arthritis among men (1, 2). Hyperuricemia is also associated with several metabolic and cardiorenovascular conditions, including diabetes and coronary artery disease (3–8). Furthermore, hyperuricemia and gout have been linked to premature mortality in some studies (9). Serum uric acid levels and the frequency of gout have been rising during the last decades (10–23), coinciding with a worsening trend of risk factor

profiles, such as obesity, metabolic syndrome, and life-style factors. Another notable change is that sugar-sweetened soft drinks and associated fructose consumption have also increased substantially over the last few decades (24–26).

In this review, we sought to summarize available epidemiologic data related to serum uric acid levels and their trends. We also discuss determinants of uric acid levels from an epidemiologic perspective, with a special focus on the data on fructose and soft drink consumption and their link to serum uric acid and associated conditions. Finally, we provide an update on comorbidities and potential outcomes of hyperuricemia, particularly metabolic-cardiovascular-renal conditions. While our focus throughout this review is on uric acid, we extend our discussion to its direct end-result, gout, wherever the relevant data are available.

Epidemiology of Uric Acid

According to the Third US National Health and Nutritional Examination Survey (NHANES III, 1988–1994) study (Table 1), the estimated mean serum uric acid concentration of the US population was 5.33 mg/dL (95% CI (5.29–5.37 mg/dL)). Overall, men had higher serum concentrations (6.06 mg/dL) than women (4.66 mg/dL) by approximately 1.4mg/dL. The mean serum uric acid concentrations did not appear to differ significantly across race/ethnicity in this nationally representative study (Table 1). While overall mean serum uric acid concentrations increased with age from 5.21 mg/dL (95% CI, 5.11–5.30mg/dL) in individuals aged 20–29 to 5.72 mg/dL (95% CI, 5.61–5.84 mg/dL) in individuals aged 80 years or older, this trend is limited to women, and is primarily driven by post-menopausal increase in serum uric acid levels (Table 2). Similar gender differences in serum uric acid levels has been reported in a Taiwanese national survey (the Nutrition and Health Survey in Taiwan [NAHSIT], 1993–96) where the mean serum uric acid concentration was 6.77 mg/dL for men, and 5.32 mg/dL for women (11).

Table 1

Prevalence of Hyperuricemia, Number of US Adults with Hyperuricemia, and Mean Serum Uric Acid Levels, NHANES III (1988–1994)

	Prevalence of Hyperuricemia**, % (95% CI)	US Adults with Hyperuricemia** (in millions)	Prevalence of Hyperuricemia (>6mg/dL), % (95% CI)	US Adults with Hyperuricemia (>6mg/dL) (in millions)	Mean Serum Uric Acid Level, mg/dL (95% CI)
Overall*	18.2 (17.1 to 19.3)	30.5	29.4 (28.0 to 30.7)	49.1	5.33 (5.29 to 5.37)
Gender					
Men	19.2 (17.8 to 20.5)	15.3	47.3 (45.2 to 49.4)	37.9	6.06 (6.01 to 6.11)
Women	17.3 (16.0 to 18.7)	15.1	12.9 (11.7 to 14.0)	11.2	4.66 (4.60 to 4.72)
Race or Ethnicity					
White	18.0 (16.8 to 19.3)	23.2	29.0 (27.3 to 30.8)	37.4	5.32 (5.27 to 5.37)
African American	22.5 (20.4 to 24.5)	3.9	31.8 (30.1 to 33.5)	5.5	5.41 (5.33 to 5.49)
Mexican American	15.2 (13.4 to 17.0)	1.3	28.8 (26.3 to 31.2)	2.4	5.26 (5.18 to 5.33)
Others	16.3 (12.7 to 19.9)	2.1	29.6 (25.8 to 33.5)	3.8	5.35 (5.22 to 5.47)
Age Category (y)					
Men					
20–29	17.5 (13.8 to 21.3)	3.2	50.8 (46.7 to 55.0)	9.3	6.10 (5.98 to 6.23)
30–39	16.6 (13.7 to 19.5)	3.3	42.9 (38.5 to 47.3)	8.5	5.96 (5.84 to 6.08)
40–49	19.5 (16.2 to 22.9)	3.1	46.1 (41.9 to 50.4)	7.2	6.04 (5.95 to 6.14)

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*Data are presented incorporating sample weights and adjusted for clusters and strata of the complex sample design of NHANES III.
**Hyperuricemia was defined as serum uric acid level > 7.0 mg/dL in men and > 5.7 mg/dL in women.

Table 2

Serum Uric Acid Trends by Age, NHANES III (1988–1994)

	Age Category (yrs)	20–29	30–39	40–49	50–59	60–69	≥ 70	P*
Men	Participants Number	1532	1368	1158	814	1120	1420	-
	Unadjusted difference mg/dl (95% CI)	0 (referent)	−0.14 (−0.31, 0.03)	−0.06 (−0.24, 0.12)	−0.05 (−0.27, 0.17)	0.02 (−0.18, 0.22)	0.10 (−0.05, 0.25)	0.174
Women	Participants Number	1737	1740	1288	952	1101	1608	-
	Unadjusted difference mg/dl (95% CI)	0 (referent)	0.01 (−0.1,0.15)	0.12 (−0.04, 0.27)	0.62 (0.47, 0.78)	0.88 (0.75, 1.02)	1.03 (0.91, 1.15)	<0.001

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*P value for linear trend.

Almost one-third of the entire US population had serum uric acid concentration >6mg/dL (49.1 million) (a widely-accepted target level of urate lowering therapy for gout (27)), whereas 11.9% had serum uric acid level >7mg/dL (19.9 million). Using the NHANES III laboratory definition of hyperuricemia (serum uric acid level > 7.0 mg/dL in men and > 5.7 mg/dL in women) (28), the prevalence of hyperuricemia in the NHANES III is 18.2%, which translates into 30.5 million of the US population (Table 1). African-Americans had the highest proportion of hyperuricemia (22.5%), followed by Caucasians (18.0%), others (16.3%), and Mexican Americans (15.2%) (Table 1). The Taiwanese NAHSIT study has shown a prevalence of 42.1% in males (serum uric acid level ≥ 7.0 mg/dL) and 27.4% in females (serum uric acid level ≥ 6.0 mg/dL) (11). Relative lack of obesity and alcohol consumption in that population suggested potential genetic or other environmental influences (11).

The serum uric acid levels have increased over the past few decades in both men (10, 12, 16, 17, 23, 29) and women (10, 17, 23, 29), according to population studies of various demographic groups (Table 3). For example, the Framingham study compared the serum uric acid levels from 1954–1958 with 1972–1976 and found a mean increase of 5.0 to 5.7 mg/dL in men and 3.9 to 4.7 mg/dL in women during the observation period (10). Similarly, The Normative Aging Study of middle-aged Caucasian men investigated the period between 1961–1980 and found the mean levels increased from below 5.5 to above 6.5mg/dL in men (12). The Coronary Artery Risk Development in Young Adults (CARDIA), which consists of African-American and Caucasian young adults aged between 24.1 to 25.6 years at baseline, found that the serum uric acid levels rose from 5.3 to 5.8 mg/dL in African-American men and 3.8 to 4.0 mg/dL in African-American women, and from 5.5 to 5.7 mg/dL in Caucasian men and 3.9 to 4.0 mg/dL in Caucasian women during 1985 to 1996 (17). A Japanese study based on young males from a university population showed an increase of serum uric acid from 5.5 to 5.76 mg/dL between 1991 and 2002 (16). Finally, a recent abstract reported that serum uric acid level increased by 0.15 mg/dL between NHANES III (1988–1994) and NHANES 2007–2008 (21), suggesting that the

increasing trend continued in the new millennium in the US. The same NHANES data comparison found a consistent increase in the prevalence of hyperuricemia during the same period (23) (Table 3). Similarly increasing trends have been reported in Japanese (16) and Chinese populations (20), although their background prevalences were lower (Table 3). Taken together, these data suggest that serum uric acid levels have increased during the past few decades. Speculation behind this increasing trend has included the increasing burden of obesity, metabolic syndrome (12, 16, 17), various life-style factors including increased alcohol consumption (12), increased prevalence of associated medical conditions (e.g. renal conditions, hypertension, and cardiovascular disorders), and increased use of medications that increase uric acid levels (low-dose aspirin or diuretics) (10).

Table 3

Secular Trends of Uric Acid Concentrations and Gout Prevalence

	Study	Follow-up Time	Age	Longitudinal Trend[a]
Mean Uric Acid	Framingham Study (10) (4^{th} exam n=5019 13^{th} exam n=3596)	US: 1954–1958 (4^{th} exam) 1972–1976 (13^{th} exam)	Range: 30–62y at 1948	Men: 5.0 → 5.7mg/dL Women: 3.9 → 4.7mg/dL
	Normative Age Study (12) (n=1,141)	US: 1961 – 1980	Mean: 42y (baseline)	Men: 5.5 → 6.5mg/dL
	CARDIA[b] Study (17) (n=2611)	US: 1985–6 – 1995–6	*African American* Men: 24y Women: 24y *White* Men: 26y Women: 26y (baseline)	*African American* Men: 5.3 → 5.8mg/dL Women: 3.8 → 4.0mg/dL *White* Men: 5.5 → 5.7mg/dL Women: 3.9 → 4.0mg/dL
	NHANES[c] Study (21) (n=18825 / 5707)	US: 1988–1994 (NHANES III)NHANES 2007–2008	Range: ≥ 20y	Overall mean change: 0.15mg/dL
	Okayama Study (16) (n=17155)	Japan: 1991–2002	Range: 18–19y	Men: 5.5 → 5.76 mg/dL
Hyperuricemia	NHANES Study (23, 29) (n= 14809 / 24693)	US: 1988–1994 (NHANES III) NHANES 1999–2008	Mean:45y (1988–1994) Mean: 47y (1999–2008)	Men: 19% → 21% (>7.0mg/dL) Women: 17% → 19% (>5.7mg/dL)
	Okayama Study (16) (n=17155)	Japan: 1991–2002	Range: 18–19y	Men: 3.5% → 4.5% (≥ 7.6mg/dL)
	Zeng et al. (20)[d] (n=502 / 7888)	China: 1980–2003	Range: ≥ 20y	Men: 1.4% → 13.8% (≥7.0mg/dL) Women: 1.3% → 6.1% (≥6.0mg/dL)
Gout	NHIS[e] Study (14)	US: 1988, 1992, 1996	Range: ≥ 18y	0.85% → 0.84% → 0.94%

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[a]Mean of percentage unless specified otherwise.
[b]CARDIA: Coronary Artery Risk Development in Young Adults.
[c]NHANES: National Health and Nutritional Examination Survey.
[d]Measured at different cities of China. The results are based on the data reported in Zeng et al.'s review article, not original studies.
[e]NHIS: National Health Interview Survey.

[f]Gout or "clinically significant" hyperuricemia.
[g]GPRD: General Practice Research Database.

This increasing trend of uric acid levels and hyperuricemia in turn has translated into an increasing disease frequency of gout in several populations (Table 3), including the US (14, 19, 30–32), UK (13) and Maori (33–35) populations. The incidence of gout appeared to increase in the US, from 45/100,000 during 1977–78 to 62.3/100,000 during 1995–96 in Rochester, Minnesota (36). A comparison analysis of NHANES data found an increase in the prevalence of gout from 2.7% (NHANES III) to 3.9% (NHANES 2007–2008) (21). The increase in prevalence of gout in the Maori populations, already known to have a higher prevalence than European populations (33), is notable, as it has increased from 27 per 1000 people to 64 per 1000 people during 1958 – 1992 (18, 33–35). A multicenter study of general practices in the United Kingdom found that the prevalence of gout in 1991 had increased 3-fold compared to the 1970s (13). Similarly, the prevalence of gout has been increasing in urban African communities (37).

Epidemiologic Evidence for Determinants of Serum Uric Acid and Gout

Demographics

Although hyperuricemia and gout have historically been considered conditions of men, and most research has focused on men, growing evidence suggests a substantial disease burden of gout among older women (14, 38). The difference in serum uric acid levels between genders (10) is likely due to the increased renal urate clearance by estrogen in women, particularly before menopause (39). A Japanese study showed a combination of estrogen and progesterone resulting in a significant drop in serum uric acid among hyperuricemic women, whereas there was no drop among controls (40). Similarly, the Heart and Estrogen-Progestin Replacement Study (HERS) reported that one year of estrogen plus progesterone therapy resulted in a slight drop in serum uric acid levels, as compared with placebo (0.2 mg/dL at one year of follow-up) (41). Finally, an NHANES III study found that menopause was associated with increased serum uric acid levels and postmenopausal hormone replacement therapy with decreased uric acid levels (42), and the Nurses' Health Study (NHS) showed consistent findings with the risk of incident gout among 92,535 women (43).

Age appears to have an influence only among women, as serum uric acid levels steadily increase with age (Tables 1, 2) (42, 44–46). In the aforementioned NHANES analysis, the increase attenuated substantially after adjusting for menopausal status, but remained significant, suggesting that menopause explains a substantial portion, but not all, of the age-associated increase among women (42). The remaining age-associated increase was explained by other age-related factors such as renal function, diuretic use and hypertension (42).

Serum uric acid levels appear to vary among race or ethnicity. African Americans have been observed to have higher serum uric acid levels than Caucasian Americans (47). This was previously linked to the increased prevalence of hypertension among African Americans (48). Also serum uric acid levels appear to be higher in aboriginal people, as observed in the Maori (18) and Taiwanese (11) aborigines, suggesting a genetic influence.

Lifestyle Factors

Lifestyle factors have an important role on the development of hyperuricemia and gout (Table 4). Various purine-rich foods and high protein intake had long been thought to be risk factors for gout (49, 50). Previous metabolic experiments in animals and humans demonstrated the urate-raising effect of

the artificial short-term loading of purified purines (51–54), whereas the possibility that the consumption of dairy products has a role in protecting against gout has been raised by previous studies (55, 56). Furthermore, the role of the Western diet has been supported by epidemiologic studies of Japanese (57) and Filipino (58) immigrants, which showed that US immigrants had higher serum urate levels than their offshore counterparts. More recently, NHANES III analyses showed that serum uric acid levels increased with increasing total meat or seafood intake, and decreased with increasing dairy intake. Furthermore, alcohol consumption increased serum uric acid levels, particularly with beer and liquor (59). These findings were replicated in the prospective analysis of the Health Professionals Follow-Up Study (HPFS, n=47,150), showing the same pattern of associations with the risk of incident gout (1, 60).

Table 4

Lifestyle Risk Factors of Hyperuricemia and Gout*

Risk Factors	Direction of Risk		
	Risk of Hyperuricemia	Risk of Gout	References
Adiposity			(2, 63, 130)
BMI	↑	↑	
Waist-to-Hip Ratio	↑	↑	
Weight Gain	↓	↓	
Weight Loss	↓	↓	
Purine-rich Foods			(1, 29)
Meats	↑	↑	
Seafoods	↑	↑	
Purine-rich Vegetables/Nuts		↔	
Alcohol	↑	↑	(59, 60)
Fructose	↑	↑	(92, 95, 102, 131)
Sugar-Sweetened Beverages	↑	↑	
Sweet Fruits/Fruit Juices	↑	↑	
Coffee/Decaffeinated Coffee	↓	↓	(68, 74)
Dairy Products			(1, 29)
Low-fat Dairy Products	↓	↓	
High-fat Dairy Products		↔	
Vitamin C Supplements	↓	↓	(77, 79–82)

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Adiposity is one of the strongest risk factors for hyperuricemia and gout (2, 12, 38, 61–64). Adiposity likely increases uric acid levels both by decreasing renal excretion of urate and in part by increasing urate production (49, 50, 65). Prospective cohort studies have found a strong relation between higher adiposity (or weight gain) and both hyperuricemia and an increased risk of incident gout (2, 12, 22, 61–64). A recent study also documented that weight reduction leads to a considerable reduction of serum urate (22). Similarly, in the Swedish Bariatric Surgery Outcome study, gastric surgery-induced weight reduction was associated with a substantially lower odds of hyperuricemia (66). Finally, the HPFS Study reported that men who had lost weight had a significantly lower risk of incident gout (63). These data collectively indicate that adiposity is a prominent determinant for hyperuricaemia and gout.

Coffee consumption may lower serum uric acid levels and the risk of gout (67, 68) in the long term via various mechanisms (69–72). For example, caffeine (1, 3, 7-trimethyl-xanthine) is a methyl-xanthine and may be a competitive inhibitor of xanthine oxidase, as demonstrated in rats (67, 69). Long-term intake of coffee and caffeine intake may also lower insulin levels (72) and increase insulin sensitivity (73). An NHANES III study and two Japanese studies found that serum uric acid levels decreased with increasing coffee intake (74–76). The HPFS (68) and NHS (67) studies also found that coffee consumption decreased the risk of gout.

Previous studies have found that high doses of vitamin C supplementation lower serum uric acid via a uricosuric effect (77–81). A double-blinded placebo-controlled randomized trial among 184 non-smoking participants showed that supplementation with 500 mg/day of vitamin C for 2 months reduced serum urate levels by 0.5 mg/dL (95% CI 0.3 to 0.6) (82). Several observational studies from Taiwan (83) and from the US (80, 84) extended the evidence for the inverse link between Vitamin C intake and the lower risk of hyperuricemia or gout.

Medical Conditions and Medications

There are many medical conditions that can elevate serum uric acid levels and the risk of gout, including hypertension, renal insufficiency, congestive heart failure and other conditions associated with severe tissue hypoxia, proliferative and inflammatory disorders associated with increased cell turnover (85). Nevertheless, large-scale epidemiologic quantification of potential impact from these conditions has been limited to several relatively common conditions, such as hypertension (or high blood pressure) and renal insufficiency (63, 64). Similarly, there are many substances and medications that can elevate serum uric acid levels and the risk of gout; however, large-scale epidemiologic data have been limited to several agents such as diuretics (63) and postmenopausal hormone therapy (42, 43).

Fructose, Hyperuricemia and Gout

Trends in Fructose Consumption

The consumption of fructose in the US has increased considerably since the introduction of high fructose corn syrup (HFCS) in 1967 (25). HFCS is a product made from corn, and usually has a composition of 42% fructose (HFCS-42) or 55% fructose (HFCS-55) (86). HFCS has several commercial advantages over crystalline sugar (sucrose), its predecessor sweetener, such as convenience to transport and use (as it is a transferable and easily mixable liquid), less dependence on foreign sources (as opposed to sugar cane, which is a tropical product) (86), and possibly being sweeter than sugar (24, 86). These properties, combined with strong marketing efforts (87) made the consumption of HFCS-containing beverages dramatically increase during the past several decades. The popularity of soft drinks in schools soared (88) and soft drinks have become the beverage of choice in the US (89). During 1977–1997 the consumption of soft drinks has increased by 61% in the US (26), which contributed to increased total caloric intake during the same periods (90).

Fructose and Serum Uric Acid

The substantial increase in soft drink and fructose consumption coincided with the increasing trend of serum uric acid (12, 17, 23, 29) and doubling of the disease burden of gout (14, 36) over the past few decades in the US (85, 91, 92)(Figure 1). Fructose is known to induce uric acid production by increasing ATP degradation to AMP, a uric acid precursor (85, 93, 94) and thus, within minutes after fructose infusion, serum uric acid levels rise (94). Furthermore, *de novo* purine synthesis is accelerated, further potentiating uric acid production.

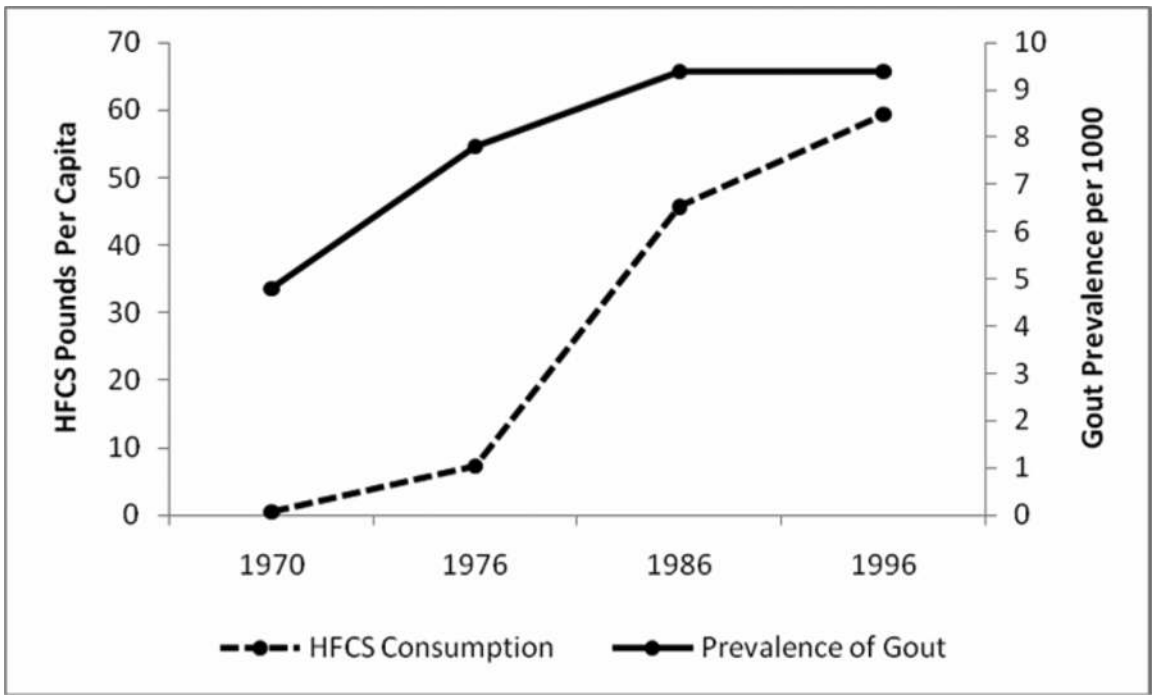

Figure 1

The relationship between high fructose corn syrup (HFCS) consumption and gout prevalence in the US

The HFCS consumption estimates are based on data from reference (26), whereas gout prevalences are based on data from references (32, 133–135) (National Health Interview Survey [NHIS]). The gout prevalence for 1970 is based on the data from 1969.

An NHANES III study showed that fructose-rich beverages, both artificial (such as soft drinks) and natural (such as orange juice), were associated with increased serum uric acid levels (95). Furthermore, nutrient fructose consumption was also positively associated with increased serum uric acid levels (difference between >75mg/day vs. <10mg/day, 0.88mg/dL). In contrast, “diet” soft drinks were not associated with serum uric acid, further supporting the notion that increased fructose consumption leads to hyperuricemia. The HPFS study found consistent links about the impact of these beverages and nutrient fructose with the outcome of gout among men (92).

Sugar Sweetened Soft Drinks, Obesity, the Metabolic Syndrome, and Diabetes

The epidemic secular trend of obesity in recent years has also coincided with the increasing use of HFCS in beverages (24). Experimental studies in animal models and from short-term feeding trials among humans have suggested that higher fructose intake contributes to insulin resistance, impaired

glucose tolerance, and hyperinsulinemia (90, 96, 97). In contrast, glucose intake had no similar adverse effects (96). Furthermore, prospective studies have reported that soft drink consumption is associated with increased risk of obesity, insulin resistance, metabolic syndrome, and diabetes (90, 98, 99). A meta-analysis based on 310,819 participants from 11 studies has also concluded that consumption of soft drinks was associated with the development of metabolic syndrome and type 2 diabetes (100). Nevertheless, these epidemiologic studies did not include the specific effects of the fructose nutrient. It remains conceivable that positive energy balance often associated with increased fructose consumption has contributed to excess adiposity (90, 101).

In addition, fructose consumption has been linked to an increased risk of hypertension and chronic renal disease. According to the NHANES III data, adolescents who drank more sugar-sweetened beverages was associated with increased systolic blood pressure (102). The NHANES 2003–2006 data similarly has shown that an increased fructose intake of ≥ 74g/day was associated with a 30% increased risk for having a blood pressure of ≥140/90 mmHg than those who had a fructose intake of <74g /day (103). However, prospective studies using the HPFS and NHS cohorts have failed to show a significant effect of fructose intake on the risk of hypertension (104).

Similar conflicting findings have been found in chronic renal disease. Data from the NHANES 1999–2004 revealed that an intake of 2+ sugary drinks / day was associated with albuminuria (OR 1.40, 95% CI(1.13–1.74)) (105). However, the Atherosclerosis Risk in Communities Study (ARIC) showed that while increased consumption of sugar-sweetened soda consumption led to an increased prevalence of chronic kidney disease, it was not associated with an increase of incident chronic kidney disease (106). From these studies, it is appears that fructose consumption is associated with prevalent, but not incident hypertension or chronic kidney disease. Why such patterns appear is not clear and the association of fructose consumption, hypertension and chronic kidney disease remains controversial.

Potential Outcomes and Associated Conditions of Hyperuricemia

Metabolic Syndrome and Diabetes

The metabolic syndrome affects more than 50 million Americans (107), and increases the risk for atherosclerotic cardiovascular disease and type 2 diabetes, as well as mortality (108). Insulin may enhance renal urate reabsorption via stimulation of urate-anion exchanger (109) and/or the Na^+-dependent anion co-transporter in brush border membranes of the renal proximal tubule (85). Higher insulin levels are known to reduce renal excretion of uric acid (110–112). A close association between serum urate levels and individual components of the metabolic syndrome has been reported (64, 113). In a representative sample of adult US men and women (NHANES III), the prevalence of the metabolic syndrome according to the same criteria increased substantially with increasing levels of serum urate from 19% for serum urate levels less than 6 mg/dL to 71% for levels of 10 mg/dL or greater (5). Correspondingly, the prevalence of the metabolic syndrome was 63% among US adults with gout versus 25% among individuals without gout. It has been suggested that hyperuricemia should be regarded as an intrinsic part (114) or surrogate marker (50, 115) for the metabolic syndrome.

Expanding on the strong associations between hyperuricemia, gout, and the metabolic syndrome, several prospective studies have reported an independent association between serum uric acid levels and the future risk of type 2 diabetes (116–119). Similarly, data from the MRFIT (Multiple Risk Factor Intervention Trial) showed that male participants with gout had a 26% increased risk for incident type 2 diabetes (4).

Cardiovascular Disease, Renal Diseases, and Mortality

Many, but not all, prospective studies reported an independent association between serum urate levels and the future risk of cardiovascular-renal outcomes and mortality and these data have been well-summarized in several reviews and meta-analysis studies (8, 85, 120–123). More recently, gout has been also linked to these outcomes, as recently reviewed (9).

A randomized clinical trial (124) and two large cohort studies (125, 126) recently showed that the use of allopurinol, a hypo-uricemic agent, could be beneficial to cardiovascular outcomes or all-cause mortality. Another previous randomized trial found reno-protective effects of allopurinol (127). Although these allopurinol benefits are correlated well with reduced uric acid levels in these studies, it is conceivable that the effect of allopurinol to lower BP may be due to the lowering of xanthine oxidase–induced oxidants, or other effects of allopurinol (124). Thus, the potential causal role of serum uric acid on these outcomes remains to be clarified further by future studies. In particular, additional randomized trial data on the effect of various urate-lowering medications (e.g. with or without xanthine oxidase inhibitor related properties) on the prevention or treatment of these outcomes would be valuable.

Conclusion

During the past few decades, the mean serum uric acid levels and the prevalence of hyperuricemia in the general population appear to have increased. Potential reasons behind these trends include the increasing prevalence of obesity and metabolic syndrome, western life-style factors, increased prevalence of medical conditions, and medication use that increase uric acid levels. In addition, the substantial increase in sugar-sweetened soft drinks and fructose consumption coincides with the secular trend of hyperuricemia and gout. These exposures appear to have several solid biologic rationales and are supported by epidemiologic data in relation to development of hyperuricemia and of gout. While sugar-sweetened beverages, a major source of fructose, are also associated with an increased risk of hypertension, and diabetes, it remains unclear whether the associations are caused by fructose *per se*, or through some other mechanism (128). Nevertheless, given their demonstrated adverse health associations and the lack of any health benefit, the evidence appears to favor minimization of sugar-sweetened beverage intake.

Footnotes

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