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Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study

Hyon K Choi,1 Gary Curhan2

ABSTRACT

Objective To examine the relation between intake of sugar sweetened soft drinks and fructose and the risk of incident gout in men.

Design Prospective cohort over 12 years.

Setting Health professionals follow-up study.

Participants 46 393 men with no history of gout at baseline who provided information on intake of soft drinks and fructose through validated food frequency questionnaires.

Main outcome measure Incident cases of gout meeting the American College of Rheumatology survey criteria for gout.

Results During the 12 years of follow-up 755 confirmed incident cases of gout were reported. Increasing intake of sugar sweetened soft drinks was associated with an increasing risk of gout. Compared with consumption of less than one serving of sugar sweetened soft drinks a month the multivariate relative risk of gout for 5-6 servings a week was 1.29 (95% confidence interval 1.00 to 1.68), for one serving a day was 1.45 (1.02 to 2.08), and for two or more servings a day was 1.85 (1.08 to 3.16; P for trend=0.002). Diet soft drinks were not associated with risk of gout (P for trend=0.99). The multivariate relative risk of gout according to increasing fifths of fructose intake was 1.00, 1.29, 1.41, 1.84, and 2.02 (1.49 to 2.75; P for trend <0.001). Other major contributors to fructose intake such as total fruit juice or fructose rich fruits (apples and oranges) were also associated with a higher risk of gout (P values for trend <0.05).

Conclusions Prospective data suggest that consumption of sugar sweetened soft drinks and fructose is strongly associated with an increased risk of gout in men. Furthermore, fructose rich fruits and fruit juices may also increase the risk. Diet soft drinks were not associated with the risk of gout.

INTRODUCTION

Conventional dietary recommendations for gout have focused on restriction of purine and alcohol intake but not sugar sweetened soft drinks.1-7 Although such drinks contain low levels of purine they contain large amounts of fructose, the only carbohydrate known to increase uric acid levels.5-7 In humans, acute administration of fructose results in a rapid increase in serum levels of uric acid through accentuated degradation of purine nucleotides1 and increased purine synthesis.2-9 This urate raising effect is exaggerated in people with hyperuricaemia2 or previous gout.2 It is unknown if this effect is sustained long term and translates into an increased risk of gout. We prospectively evaluated the relation between intake of sugar sweetened soft drinks and fructose and the incidence of gout in a cohort of men with no history of gout.

METHODS

The health professionals follow-up study is an ongoing study of 51 529 professional men (see bmj.com). The participants completed a questionnaire in 1986 on diet, medical history, and drugs. Of the 49 166 men who provided information on intake of sugar sweetened soft drinks, 2773 (5.6%) had had gout and were excluded.

To assess dietary intake we used a food frequency questionnaire on the average use of over 130 foods and beverages during the previous year.10-12 The baseline questionnaire was completed in 1986 and updated every four years. On all questionnaires participants were asked how often during the previous year they had consumed sugar sweetened soft drinks, diet soft drinks, different types of fruits, and fruit juices. We summed the intake of items to create a total for consumption. We computed nutrient intakes by multiplying the frequency response (see bmj.com) by the nutrient content of the specified portion sizes.11 Fructose is a monosaccharide. Half of the disaccharide sucrose is fructose, and therefore total fructose intake is equal to the intake of free fructose plus half the intake of sucrose.

At baseline and every two years participants provided information on weight, regular use of drugs, and medical conditions.11 We ascertained incident cases of gout using the survey criteria of the American College of Rheumatology.13 Briefly, on each biennial questionnaire participants indicated whether they had received a diagnosis of gout from a doctor. We sent a supplementary questionnaire to participants with self reported gout to confirm the report and to ascertain the American College of Rheumatology criteria for gout.14-17 Our primary end point was incident cases of gout meeting six or more of the 11 criteria.
Statistical analysis

We computed person time of follow-up for each participant from the return date of the 1986 questionnaire to the date of diagnosis of gout, death from any cause, or the end of the study period (1998), whichever came first.

To represent long term dietary intake patterns of individual participants we used cumulative average intakes on the basis of the information from questionnaires completed in 1986, 1990, and 1994. We used Cox proportional hazards modelling to estimate the relative risk for incident gout in all multivariate analyses. For these analyses we categorised soft drink consumption into six groups: <1 serving monthly, 1 serving monthly to 1 weekly, 2-4 servings weekly, 5-6 servings weekly, 1 serving daily, and ≥2 servings daily. We categorised free fructose and total fructose intake into fifths for percentage of energy. Multivariate models for soft drink consumption were adjusted for age, total energy intake, alcohol intake, body mass index, use of diuretics, history of hypertension, history of chronic renal failure, and average daily intake of meats, seafood, purine rich vegetables, dairy foods, and total vitamin C. We evaluated the potential impact of coffee intake, caffeine intake, and fructose intake by entering each term into the multivariate model for soft drink consumption. In multivariate nutrient density models for fructose intake, we simultaneously included energy intake, the percentages of energy derived from protein and non-fructose carbohydrate, intake of vitamin C and alcohol, and other non-dietary variables. The coefficients from these models can be interpreted as the estimated effect of substituting a specific percentage of energy from fructose for the same percentage of energy from non-fructose carbohydrate (or fat).

To assess possible effect modification we did analyses stratified by body mass index (<25 v ≥25 kg/m²), alcohol use (yes or no), and dairy intake (<1.6 v >1.6 servings/day). We tested the significance of the interaction with a likelihood ratio test by comparing a model with the main effects of each intake and the stratifying variable and the interaction terms with a reduced model with only the main effects. For relative risks we calculated 95% confidence intervals. P values are two sided.

RESULTS

During 12 years of follow-up of 46 393 eligible men from the health professionals follow-up study, we documented 755 newly diagnosed cases of gout meeting the American College of Rheumatology criteria. With increasing consumption of sugar sweetened soft drinks the intake of caffeine, fructose, meats, and high fat dairy foods tended to increase whereas mean age and low fat dairy intake tended to decrease (see bmj.com). With increasing consumption of free fructose the body mass index and intake of alcohol, caffeine, meats, and high fat dairy foods tended to decrease (see bmj.com).

Sugar sweetened soft drinks and incident gout

Increasing intake of sugar sweetened soft drinks was associated with an increasing risk of gout (see bmj.com). Compared with the reference consumption level of less than one serving monthly, the multivariate relative risk of gout for 5-6 servings weekly was 1.29 (95% confidence interval 1.00 to 1.68), for one serving daily was 1.45 (1.02 to 2.08), and for two or more servings daily was 1.85 (1.08 to 3.16; P for trend 0.002). Diet soft drinks were not associated with risk of gout (P for trend 0.99). When additional adjustments were made for caffeine intake or coffee intake these results did not change materially. After adjustment for fructose in intakes of fifths, however, the association between the intake of sugar sweetened soft drinks and risk of gout was attenuated and no longer significant (P for trend 0.10).

Fructose intake and incident gout

Increasing fructose intake was associated with an increasing risk of gout (see bmj.com). Compared with men in the lowest fifth of free fructose intake, the multivariate relative risk of gout in the highest fifth when substituting fructose for the equivalent energy from fat was 1.81 (95% confidence interval 1.38 to 2.38; P for trend <0.001). The corresponding relative risk increased after adjustment for total carbohydrate intake to reflect the substitution effect of fructose for other types of carbohydrates (multivariate relative risk 2.02, 1.49 to 2.75; P for trend <0.001). Similarly, higher total fructose intake was significantly associated with increasing risk of gout (P for trend ≤0.001; see bmj.com).

Among other items contributing fructose, total fruit juice intake was associated with risk of gout (see bmj.com). Compared with men who consumed less than a glass of fruit juice a month, the multivariate relative risk for gout in those consuming two or more glasses daily was 1.81 (95% confidence interval 1.12 to 2.93; see bmj.com). The corresponding multivariate relative risk for orange juice or apple juice was 1.82 (1.11 to 3.00). Similarly, intake of oranges or apples was associated with risk of gout. Compared with men who consumed less than one apple or orange a month, the multivariate relative risk of gout in those who consumed one apple or orange daily was 1.64 (1.05 to 2.56). The corresponding multivariate relative risk for orange intake alone was 1.55 (1.02 to 2.36) and for apple intake alone was 1.48 (0.98 to 2.25).

Risk according to body mass index, alcohol use, and dairy intake

Stratified analyses were done to evaluate whether the association between consumption of sugar sweetened soft drinks and fructose and risk of gout varied according to body mass index, alcohol use, and dairy intake. Relative risks from these stratified analyses consistently suggested associations similar to those from the main analyses, and no significant interaction was found with these variables (all P values for interaction >0.63; see bmj.com).
Other definitions of dietary exposure and gout
The multivariate relative risk between the extreme fifths of free fructose substituting for other carbohydrates with baseline dietary intake was 1.81 (95% confidence interval 1.36 to 2.41; P for trend <0.001) and with updated information without cumulative averaging was 1.93 (1.44 to 2.60; P for trend <0.001). The corresponding multivariate relative risks for substituting free fructose for fat were 1.59 (1.23 to 2.06; P for trend <0.001) and 1.77 (1.35 to 2.31; P for trend <0.001).

With other case definitions of gout, the magnitudes of associations tended to increase as specificity of the case definition increased, but null associations remained null (see bmj.com).

DISCUSSION
In this large prospective study of men we found that the risk of incident gout increased with increasing intake of sugar sweetened soft drinks. The risk was significantly increased at an intake of 5-6 servings weekly and rose with increasing intake. The risk of incident gout was 85% higher among men who consumed two or more servings of sugar sweetened soft drinks daily compared with those who consumed less than one serving monthly. In contrast, diet soft drinks were not associated with the risk of incident gout. Furthermore, the risk of gout was significantly increased with increasing fructose intake; the risk of gout was about twice as high among men in the highest fifth of free fructose consumption than among men in the lowest fifth. These associations were independent of dietary and other risk factors for gout such as body mass index, age, hypertension, diuretic use, alcohol intake, and history of chronic renal failure.

We found that the risk of incident gout associated with fructose or fructose rich foods was substantial. Similarly, the magnitudes of risk posed by sugar sweetened soft drinks or fruit juices were slightly larger than that of spirits (relative risk for ≥2 servings a day, 1.60) in the same cohort.15

Interestingly, fructose shares ethanol’s urate raising mechanism that induces uric acid production by increasing ATP degradation to AMP, a precursor of uric acid.49,10-21 Fructose phosphorylation in the liver uses ATP, and the accompanying phosphate depletion limits regeneration of ATP from ADP, which in turn serves as substrate for the catabolic pathway to uric acid formation.22 In conjunction with purine nucleotide depletion, rates of purine synthesis de novo are accelerated, thus potentiating uric acid production.8 In contrast, glucose and other simple sugars do not have the same effect.3

Fructose could also indirectly increase the level of serum uric acid by increasing insulin resistance and circulating insulin levels.23 For example, reductions in insulin binding and insulin activity were observed among healthy people fed 1000 extra kilocalories as fructose for seven days, whereas intake of 1000 extra kilocalories as glucose had no similar adverse effects.24 Likewise, in another study in humans, intake of 15% of total energy as fructose for five weeks resulted in higher insulin and glucose responses than isocaloric diets with 7.5% of energy from fructose or no fructose.

Public health implications
Conventional dietary recommendations for gout have focused on restriction of purine intake, although low purine diets are often high in carbohydrate, including fructose.1 Our data provide prospective evidence that fructose poses a substantial risk for gout. These data even suggest that the risk posed by free fructose intake could be at least as large as that by purine rich foods such as meat.12 Thus the conventional low purine diet approach allowing fructose intake could worsen the overall net risk of gout attacks. Also, because fructose intake is associated with increased serum insulin levels, insulin resistance, and increased adiposity the overall negative health impact from fructose is expected to be larger particularly in patients with gout, who often have the metabolic syndrome26 and are overweight.12 These findings support the importance of recommending a reduction in fructose intake in patients with hyperuricaemia and gout in order to reduce the risk of gout as well as to improve overall long term outcomes. Correspondingly, prospective cohort data indicate that higher consumption of sugar sweetened drinks is associated with excess adiposity and risk of type 2 diabetes.27,28 In contrast, higher consumption of fruits (and vegetables) is associated with a lower risk of major chronic disorders29 such as coronary heart disease.30 These various benefits and risks associated with individual fructose rich food items should be carefully considered in the potential public health applications of our findings.

Strengths and limitations
Our study prospectively collected and validated data on exposure and avoided potential recall bias because the data on intake were collected before the diagnosis of gout. Because dietary consumption was self reported, some misclassification is inevitable. The food frequency questionnaire was validated in a sample of this cohort and any remaining misclassification would have likely biased the results towards the null. The use of repeated dietary assessments not only accounts for changes in consumption over time but also decreases measurement error.10 In our study fulfilment of six of the 11 criteria for gout from the American College of Rheumatology survey14 showed a high degree of concordance with the review of medical records,13 and the incidence rate of gout fulfilling the criteria in our cohort closely agreed with that estimated among male doctors in the Johns Hopkins precursor study (1.5 ± 1.7 per 1000 person years).15 Furthermore, when we evaluated the impact of various definitions for gout our findings were robust and the magnitudes of associations tended to increase with increasing specificity of the case definition. Our findings are most directly generalisable to men aged 40 and older with no history of gout.
WHAT IS ALREADY KNOWN ON THIS TOPIC
Sugar sweetened soft drinks contain large amounts of fructose, which is known to increase serum uric acid levels. No studies have investigated the link between these beverages and fructose intake and the risk of gout.

WHAT THIS STUDY ADDS
Consumption of sugar sweetened soft drinks or fructose is associated with an increased risk of gout in men. Diet soft drinks are not associated with the risk of gout in men.

In conclusion, our findings provide prospective evidence that consumption of sugar sweetened soft drinks and fructose is strongly associated with an increased risk of gout. Furthermore, fructose rich foods and fruit juices may also increase the risk. Diet soft drinks were not associated with the risk of gout.

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Competing interests: None declared.

Ethical approval: This study was approved by the Partners HealthCare System institutional review board; return of a completed questionnaire was accepted by the board as implied informed consent.

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