Original Article

Effects of fructose from apple and honey on serum uric acid in young Chinese: Randomized crossover trials

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Background and Objectives: Overconsumption of drinks containing fructose increases the risk for hyperuricemia and gout. Comparative analysis evaluating the indicators of serum uric acid (SUA) load caused by natural food-derived fructose and pure fructose in sweeteners is lacking. We aimed to uncover the effect of fructose from apple and honey and pure fructose powder on the SUA concentration of healthy young Chinese individuals. **Methods and Study Design:** Two randomized crossover trials were performed. The participants were randomly assigned to consume apple or honey (test food) or pure fructose powder (reference food); one week later, the groups' dietary intervention was switched. Blood samples were collected at 0, 30, 60, and 120 min after meal to measure the SUA and blood glucose concentrations. **Results:** At 30 and 60 min, the SUA concentration in participants consuming apple or honey was lower than in those consuming fructose powder. At 120 min, the SUA concentration of participants consuming apple returned to baseline. The areas under the curve (AUC) within 2 h (2h-AUCs) of SUA exhibited the trend of fructose >honey >apple. The 2h-AUC ratio between test food and reference food was determined using the uric acid index to assess the efficiency of food-derived fructose in increasing the SUA concentration. The uric acid index of honey was higher than that of apple. Men had higher postprandial SUA concentration than women. **Conclusions:** Food-derived fructose caused a lighter load on uric acid metabolism than pure fructose. Uric acid index can be useful for distinguishing fructose-containing foods.

Key Words: serum uric acid, uric acid index, fructose, apple, honey

INTRODUCTION

Uric acid in blood at low concentration exerts an antioxidative effect according to the human and animal data; however, in excessive amounts, it crystallizes and acts as a pro-oxidant, thereby inducing gout.[1] To date, chronic hyperuricemia is accepted as an independent risk factor for gout,[2] rheumatoid arthritis,[3] nonalcoholic fatty liver disease, diabetes,[4-6] and even some types of cancers.[7,8]

Uric acid is not only derived from the breakdown of purines, but also from fructose metabolism. The hepatic metabolism of fructose leads to the rapid depletion of ATP and increased production of uric acid.[9-12] In the modern food industry, a sweetener rich in fructose is often used in processed foods, including sweetened foods and beverages, since fructose is the sweetest naturally occurring carbohydrate.[13] High fructose corn syrup (HFCS) is a man-made flavored syrup containing a high proportion of fructose and is widely used in manufactured foods. Participants consuming HFCS-sweetened beverage reportedly had higher serum uric acid (SUA) concentration than those consuming sucrose-sweetened beverage. Data from previous prospective cohort studies reported a positive association between the intake of fructose-rich beverages and an increased risk of gout or hyperuricemia in men and women.14,15 A previous meta-analysis showed that the risk of hyperuricemia is positively correlated with the intake of fructose (odds ratio: 1.85; 95% confidence interval: 1.66–2.07).[16] Moreover, a larger body of evidence, including from animal experiments,[17,18] epidemiological studies, and clinical trials, supports that sugary drinks with HFCS also increase the risk of obesity, hypertension, insulin resistance, fatty liver, and dyslipidemia. Therefore, limiting the intake of HFCS is largely recommended.[19-21]

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Notably, fruits and honey are the main sources of natural fructose.[22] The Brisighella Heart Study based on the Mediterranean cohort showed that people who consumed large amounts of fruits had elevated SUA concentration and increased incidence of hypertension and diabetes,[23] low-density lipoprotein oxidation,[24] arterial stiffness,[25] impaired cognitive function,[26] and heart failure.[27] The overconsumption of fructose even from fruits is suggested to be harmful. However, increasing the intake of fruits is recommended by health organizations worldwide as they are low energy-dense foods that are rich in fiber and micronutrients.[28] Therefore, a method for assessing the capacity of fruits to increase the SUA concentration is warranted. Honey is a sweet and viscous food substance. It is often used for cooking and baking, or as a spread on bread in Western countries; it is also used in some commercial beverages such as tea drink in China.

This study aimed to compare the effect of fructose from apple, honey, and pure fructose powder on the SUA concentration of healthy young Chinese individuals and explore a method to evaluate the load on uric acid metabolism caused by natural food-derived fructose.

METHODS

Study design

The study was performed at the School of Medicine, Ningbo University, from September to October 2020. Two randomized crossover trials, apple trial and honey trial, were carried out: apple or honey was used as test food, while a commercial pure fructose powder was used as a reference food. In the apple trial, the participants were randomly assigned to consume apple (test food) or pure fructose powder (reference food) at the first stage, and received an alternative dietary treatment at the second stage after a washout period of one week. In the honey trial, the test food was honey, while the reference food was pure fructose powder; the participants received the dietary intervention following the same principle. If the sample size is 16 persons, an 80% power is required to detect a difference of 1 standard deviation (SD) in plasma uric acid response to treatment at an α level of 0.05, since 20% of the participants is expected to drop out from the study. Therefore, the sample size exceeds 20 persons.[29]

Participants

College students were recruited from Ningbo University. Participants 1) aged 18–26 years, 2) with a fasting blood glucose concentration of <6.1 mmol/L, and 3) with a body mass index of <24 kg/m^2 according to the recommendation of the China Nutrition Society were included in this study. Participants with 1) menstruation and 2) chronic diseases, including diabetes, hypertension, cancers, digestive disorders, gout, and hyperuricemia, which was defined as a fasting SUA of >416.5 μmol/L (men) or 357 μmol/L (women) on two tests were excluded.30 Written informed consent was obtained before the trials were conducted. The experiment was approved by the Ethics Committee of School of Medicine, Ningbo University (Ningbo, China), and registered in the Chinese Clinical Trial Registry at http://www.chictr.org.cn/ (registration number: ChiCTR2000036443).

Trial foods

The same batch of red Fuji apples and Guanshengyuan honey produced by a local manufacturer were used as test foods. Fructose powder with a purity of ≥99% was purchased from Shandong Xiwang Sugar Co. (Shandong, China) and was used as the reference food. At the beginning of trial, honey, fructose powder dissolved in 50 mL warm water, and fresh apple pulp were provided to the participants.

Measurement of fructose in foods using HPLC

HPLC reagents and conditions

The amount of fructose, glucose, and sucrose in foods was measured using high-performance liquid chromatography (HPLC) according to the China National Standard protocol GB 5009.8-2016. A Waters 2695 HPLC apparatus equipped with 2414 differential refractive index detector (Waters Corp, USA) was used. Glucose, fructose, and sucrose standard substances were purchased from Chem Service (West Chester, USA). Zinc acetate and potassium ferrocyanide of analytical grade were purchased from Sinopharm Chemical Reagent Co., Ltd (Shanghai, China). A 20 μL sample was injected into a Kromasil 100A NH2 column at a temperature of 40 °C (250 × 4.6 mm, 5 μm; Kromasil) and detected using a refractive index detector at a temperature of 35 °C. The elution was performed using acetonitrile and water (75:25, v/v) at a flow rate of 1.0 mL/min.

Sample preparation

Three randomly chosen red Fuji apples were equally divided into three layers (inner, middle, and outer) after removal of peels and seeds. Equal amounts (5 g) of flesh from each layer of the three apples were mixed with the solution (2.5 mL of zinc acetate solution [$Zn(CH_3COO)_2 \cdot 2H_2O$], 2.5 mL of potassium ferricyanide solution {$K_4[Fe(CN)6] \cdot 3H_2O$}, and 45 mL of ultra-pure water) and shaken for 60 min. After centrifugation at 9,500 rpm for 5 min, the mixtures were filtered through a 0.22-μm nylon filter (Millipore). Honey (30 g) from three individual bottles was directly added to sterile tubes.

Calibration curve

A series of dilutions with concentrations of 0.4, 2.0, 5.0, 10.0, and 20.0 mg/mL were prepared and then detected by HPLC to establish the calibration curve of fructose, glucose, and sucrose. The calibration curve was plotted with the peak area on the vertical (Y) axis and the standard concentrations on the horizontal (X) axis using linear regression.

Study protocol

The participants were prohibited from drinking alcohol, consuming oversized animal meat, eating desserts, or staying up late the day before the test. All participants fasted from 10:00 pm the day before the test. On the actual test day, they arrived at the scene at 08:00 am. The height, body weight, and blood pressure of the participants were recorded. Then, the dietary treatment was administered orally. During the dietary intervention, all participants were asked to consume their food within 10 min. Three milliliters of venous blood samples were collected

at 0, 30, 60, and 120 min in order to analyze the uric acid concentration. Blood pressure was also measured at 120 min.

Statistical analysis

All data were analyzed using SPSS 24.0 software (Chicago, IL, USA). The parameters obtained at 0 min of dietary intervention, uric acid index, and 2h-AUC of SUA are expressed as mean ± Standard deviation (SD), while other data were presented as mean ± standard error of means (SEM). The differences in the SUA and blood glucose concentrations between 0 min and 30 min or between 30 and 120 min after a specific treatment were analyzed using repeated measures of the general linear model, while the values obtained at 0 min were adjusted as covariates to avoid the interference of differences between individuals; the sequence of dietary intervention and participants as random effects were adjusted. The 2h-AUC of serum uric acid and blood glucose after administering the dietary treatment were calculated using the trapezoidal rule (GraphPad Prism 8.0.1, San Diego, CA, USA). The normality of variables such as 2h-AUC of uric acid, 2h-AUC of blood glucose, and the changes in blood pressure (both diastolic and systolic) from 0 min to 120 min was assessed using the Shapiro-Wilk test. Normalized and non-normalized data were analyzed using one-way analysis of variance and non-parametric test, respectively. Independent-samples t-test was used to determine the uric acid index. A two-tailed p value of <0.05 was considered statistically significant.

RESULTS

Quantification of fructose with HPLC

The result of HPLC showed that 1 g of Fuji apple provides 0.110 g of fructose (0.096 g of free fructose, 0.041 g of glucose, and 0.0311 g of sucrose comprising 0.014 g of glucose and 0.014 g of fructose), while 1 g of honey has 0.489 g of free fructose and 0.442 g of glucose. Considering the feasibility of intake, the dose of fructose consumed was 25 g, which is equivalent to 222 g of flesh from a medium-sized apple or 51 g of honey.

Anthropometric characteristics of the participants

A flow chart of the study is presented in Figure 1. Twenty-nine and thirty-five college students aged 22–26 years were enrolled in the apple trial (n=29) and honey trial

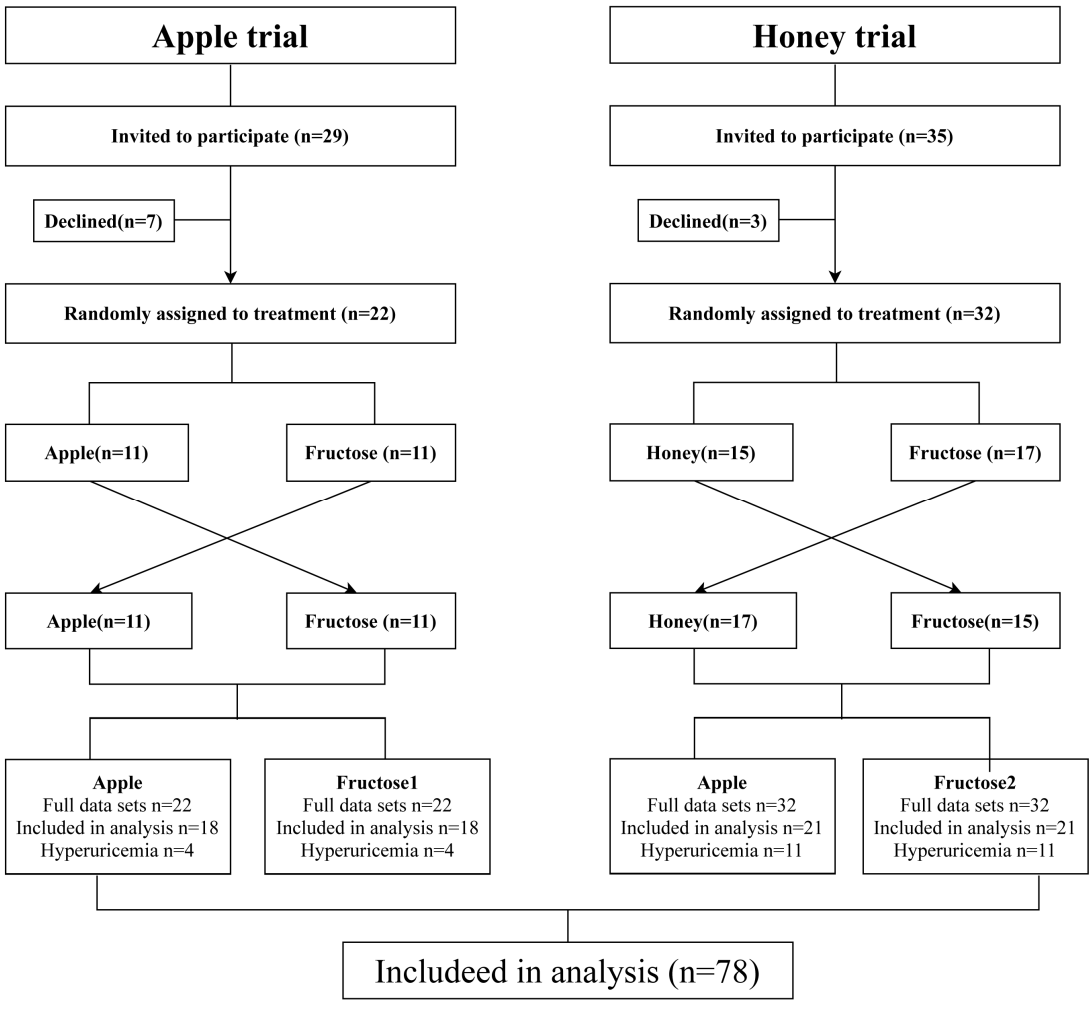

Figure 1. The Consolidated Standards of Reporting Trials diagram of the participant recruitment process. Sixty-four college students (apple trial, n=29; honey trial, n=35) aged 22–26 years were enrolled. Prior to the administration of the dietary intervention, seven (men) and three (two men and one woman) volunteers dropped out of apple trial and honey trial, respectively, due to unrelated personal reasons. Four participants (three men and one woman) in the apple trial and 11 participants (eight men and three women) in the honey trial were excluded from the analysis owing to the occurrence hyperuricemia. Overall, 78 full datasets were included in the study.

(n=35), respectively. Prior to the administration of the dietary intervention, seven (men) and three (two men and one woman) volunteers dropped out of the apple trial and honey trial, respectively, due to unrelated personal reasons. Four participants (three men and one woman) in the apple trial and 11 participants (eight men and three women) in the honey trial were excluded owing to the occurrence of hyperuricemia. The anthropometric characteristics of participants at baseline are summarized in Table 1; no difference was found in all measured parameters at baseline among the participants.

SUA concentration of participants

The changes in SUA concentration of all participants consuming apple, honey, and fructose powder are depicted in Figures 2A and Table 2. As shown in Figures 2A, the SUA concentration of participants after consumption of apple rapidly peaked during the first 30 min, but then gradually decreased to the lowest at 120 min; meanwhile, the SUA concentration of participants consuming honey continuously increased. Of note, the curves of SUA over time after fructose powder and apple consumption had the same shape but different amplitude. After comparing SUA concentration at different time points, results showed that the fructose powder intake induced a significant increase in SUA concentration at 30 and 60 min compared with that at 0 min (fructose (apple trial): $p_{30min}<0.001$, $p_{60min}<0.001$; fructose (honey trial): $p_{30min}<0.001$, $p_{60min}<0.001$). However, no significant difference was found between the SUA concentrations at 30 and 60 min after consuming apple and honey and the SUA concentration at 0 min (apple: $p_{30min}=0.075$, $p60min=0.148$; honey: $p_{30min}=0.057$, $p_{60min}=0.052$). In our study, the difference between SUA test food and SUA reference food (i.e., SUA test food – SUA reference food) of each participant at the same time points after meal was calculated to compare the body's response to fructose derived from different sources. As shown in Table 2, all the values of the SUA test food and SUA reference food at 30 min and 60 min for the apple trial and honey trial were negative. Results of the statistical analysis showed that the SUA concentration of women at 30 min and 60 min after consuming apple were significantly lower than those of fructose ($p_{30min}=0.01$, $p_{60min}=0.02$).

Moreover, men had a stronger response to fructose intake than women, with a higher concentration of SUA at the same time point compared with women, as illustrated in Figure 2B and Figure 2C. The difference between SUA men and SUA women (SUA men–SUA women) was used to quantitatively evaluate the effect of gender on uric acid metabolism. As shown in Table 3, the SUA concentrations of men at 60 min and 120 min were higher than that of women, and a significant difference in SUA was observed between women and men at 120 min after fructose intake in the honey trial ($p=0.04$).

Then, the 2h-AUC of SUA after dietary fructose loading was measured. As shown in Table 4 and Figure 2D and 2E, male and female participants consuming apple and honey had lower 2h-AUC of SUA than those consuming fructose powder. The 2h-AUC of SUA of men consuming apple and honey was significantly higher than that of women (p value for apple intake: was 0.005, p value for honey intake: 0.015). In terms of SUA concentration, men exhibited a stronger response to fructose-containing foods than women. The gender-related difference in fructose treatment almost disappeared when the participants consumed fructose powder.

In this study, a new metabolic parameter was introduced, uric acid index, which was defined as the ratio of $2h\text{-}AUC_{test\ food}$ to $2h\text{-}AUC_{reference\ food}$, to assess the uric acid metabolic load caused by specific food-derived fructose. Both test food and reference food provided 25 g of fructose. Therefore, the uric acid index was calculated and compared using the independent samples t-test. The uric acid index of honey was higher than that of apple, although no significant difference in the uric acid index was observed between apple and honey ($p=0.153$) as depicted in Figure 3F and Table 5. For either men or women, no significant difference was also found in the uric acid index of apples and honey ($p_{women}=0.294$, $p_{men}=0.419$).

Blood glucose measurement

As depicted in Figure 3A, the blood glucose concentration increased significantly at 30 min after the intake of honey and apple, while it only slightly increased after consumption of fructose powder. The highest blood glucose concentration (5.55 μmol /L) was observed in the apple-treated group at 30 min, and no difference was observed in the blood glucose concentration between the honey group and apple group ($p=0.151$). Relatively, the blood glucose concentration of participants who consumed fructose powder was the lowest. At 60 min, the blood glucose concentration of participants who consumed honey was the highest ($p<0.001$), while those of participants who consumed apple and fructose powder had similar blood glucose concentration. The 2h-AUC of blood glucose was also calculated. The 2h-AUC of honey was significantly higher than that of apple and fructose

Table 1. Anthropometric characteristics of participants†

Parameters	Apple trial		Honey trial	
	Apple (n=18)	Fructose (n=18)	Honey (n=21)	Fructose (n=21)
Age (y)	22.5±2.2	22.5±2.2	22.8±1.7	22.8±1.7
women, n (%)	12 (66.7)	12 (66.7)	12 (57.1)	12 (57.1)
men, n (%)	6 (33.3)	6 (33.3)	9 (42.9)	9 (42.9)
BMI ($kg/m^{2)}$	20.7±1.72	20.7±1.72	20.2±2.05	20.2±2.05
Systolic blood pressure (mm Hg)	116±11.6	115±10.18	110±8.54	111±11.3
Diastolic blood pressure (mm Hg)	78.4±9.00	80.2±8.33	70.8±7.96	70.1±7.66
Blood glucose (mmol/L)	4.09±0.38	4.17±0.24	4.17±0.61	3.92±0.57

DBP: diastolic blood pressure; SBP: systolic blood pressure.
†Data were obtained at 0 min of dietary intervention and presented as mean±SD.

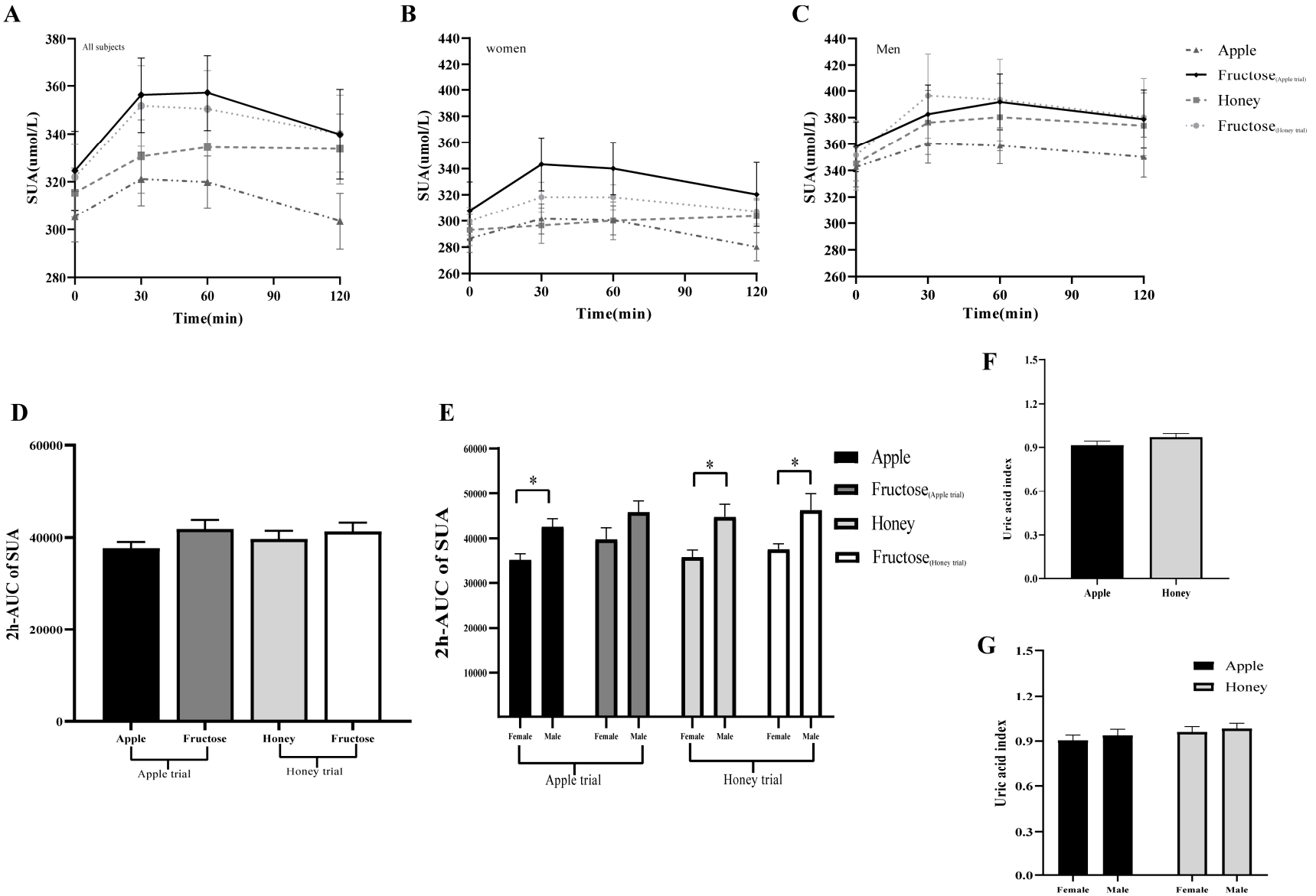

Figure 2. Serum uric acid (SUA) concentration after consuming 25 g of fructose derived from different sources. A: SUA concentration of all participants at 0 min, 30 min, 60 min, and 120 min. B: SUA of women at 0 min, 30 min, 60 min, and 120 min. C: SUA of men at 0 min, 30 min, 60 min, and 120 min. D: Area under the curve (AUC) for SUA in all participants. E: AUC for SUA in women and men. F: Uric acid index in all participants. G: Uric acid index in women and men. $^{*}p<0.05$.

Table 2. Serum uric acid concentration at different time points after food intervention[†]

		SUA at 0min, μmol/L[‡]			SUA test food –SUA reference food, μmol/L[‡]					
	Gender	SUA Test Food	SUA Reference food	n	30 min	$p^{§}$	60 min	$p^{§}$	120 min	$p^{§}$
Apple trail	women	287±37.0	308±75.8	24	-22.5±8.41*	0.01	-20.6±7.74*	0.02	-18.6±10.4	0.09
	men	343±36.8	358±45.8	12	-6.91±11.3	0.56	-18.2±9.03	0.07	-12.4±9.00	0.20
	All subjects	305±13.5	325±13.5	29	-35.2±22.5	0.54	-37.3±22.3	0.63	-36.3±22.7	0.51
Honey trail	women	293±40.8	300±36.8	24	-13.5±7.45	0.08	-12.0±7.97	0.15	2.80±6.48	0.67
	men	345±39.2	351±78.6	18	-12.6±16.9	0.47	-5.80±20.3	0.78	1.05±17.4	0.95
	All subjects	315±12.5	323±12.8	42	-22.3±21.1	0.88	-18.7±20.9	0.89	-6.39±21.3	1.00

[†]Participants with complete data (0 min, 30 min, 60 min, and 120 min) and normal uric acid concentration (men: <416.4 μmol/L; women: <356.9 μmol/L) were enrolled.
[‡] Data at 0 min were presented as mean ± SD; results at 30 min, 60 min, and 120 min were presented as mean ± SEM.
[§]General linear model: repeated measures analysis was used to compare the effects of dietary treatments. The treatments were considered as fixed effects, while the participants were considered as random effects; values at 0 min were included in the model as covariates.
*p<0.05.

Table 3. Comparison of SUA concentration at different time points after meal by gender[†]

	Foods	n	SUA men –SUA women at 30 min[‡]	$p^{§}$	SUA men –SUA women at 60 min[‡]	$p^{§}$	SUA men –SUA women at 120 min[‡]	$p^{§}$
Apple trail	Apple	18	2.69±7.92	0.74	5.09±8.38	0.55	18.7±9.95	0.08
	Fructose	18	-5.36±13.4	0.70	7.19±11.3	0.54	5.54±14.6	0.71
Honey trail	Honey	21	13.0±16.1	0.43	12.5±19.0	0.52	5.30±16.5	0.75
	Fructose	21	22.0±11.8	0.08	21.0±12.8	0.12	21.4±10.6*	0.04

[†]Participants with complete data (0 min, 30 min, 60 min, and 120 min) and normal uric acid concentration (men: <416.4 μmol/L; women: <356.9 μmol/L) were enrolled.
[‡]Results at 30 min, 60 min, and 120 min were presented as mean ± SEM.
[§]General linear model: repeated measures analysis was used to compare the SUA concentrations at different time points of food intake by gender. Gender was considered as fixed effects, while the participants were considered as random effects; values at 0 min were included in the model as covariates.
*p<0.05.

Table 4. 2h-AUC of SUA of apple, honey by gender[†]

	FOODS	2h-AUC men[‡]	2h-AUC women[‡]	n	$p^{§}$
Apple trail	Apple	42595±4222**	35270±4562	18	0.005
	Fructose	45828±6044	39824±8748	18	0.153
Honey trail	Honey	44788±8285*	35899±5350	21	0.015
	Fructose	46273±10731*	37609±4065	21	0.047

[†]AUC of uric acid was calculated by GraphPad Prism software using the trapezoidal method.
[‡]All data were presented as mean±SD.
[§]The normality of data distribution was assessed using Shapiro-Wilk test. The data with normal and non-normal distribution were analyzed using one-way analysis of variance and non-parametric test, respectively.
*p<0.05, **p<0.01 when compared to 2h-AUC women.

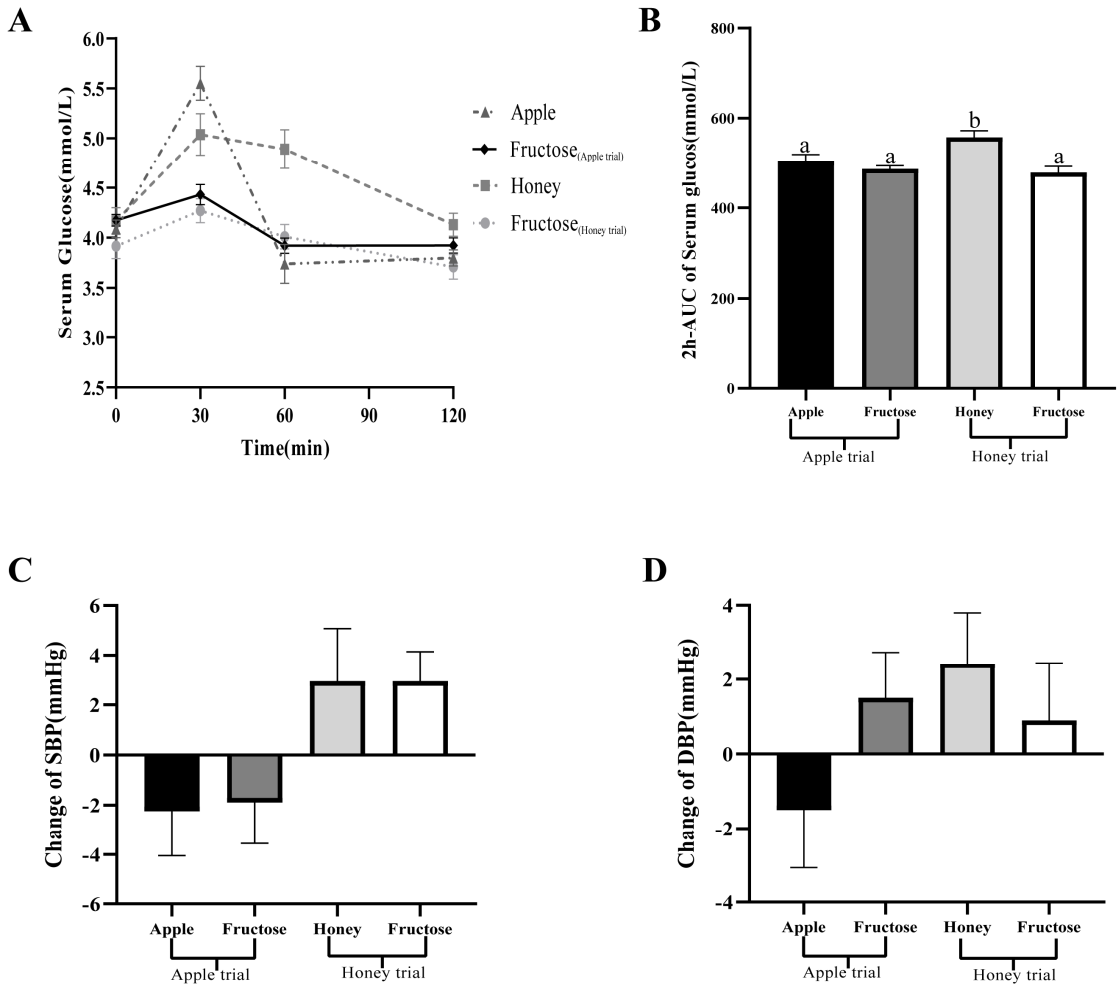

Figure 3. Effect of apple, honey, and fructose consumption on blood glucose and blood pressure. A: Blood glucose concentration at 0 min, 30 min, 60 min, and 120 min. B: Area under the curve of blood glucose. C and D: Changes in systolic blood pressure and diastolic blood pressure between 0 min and 120 min. Values without a common superscript are significantly different; $p<0.05$.

Table 5. The uric acid index of apple and honey

Gender	Testing Food	n	Uric acid index†	p‡
Woman	Apple	12	0.90±0.12	0.294
	honey	12	0.96±0.13	
Men	Apple	6	0.94±0.10	0.419
	honey	9	0.98±0.10	
All subjects	Apple	18	0.91±0.12	0.153
	honey	21	0.97±0.12	

All data were presented as mean±SD.
†Uric acid index was newly defined as the ratio of 2h-AUC of the test food (contain 25 g fructose) to that of the reference food (pure fructose powder, 25g).
‡The normality of data distribution was assessed using Shapiro-Wilk test. The data with normal and non-normal distribution were analyzed using independent-samples T-test and non-parametric test, respectively.

($p<0.01$), as shown in Figure 3B.

Blood pressure evaluation

The effect of food containing fructose on blood pressure is shown in Figure 3C and 3D. No significant difference was observed in the change in diastolic or systolic blood pressure after the ingestion of foods, although the consumption of apples tended to reduce the systolic and diastolic blood pressure.

DISCUSSION

Earlier studies have shown that purine-rich foods such as meat, seafood, and alcohol are important dietary factors contributing to the development of hyperuricemia.[31] In recent decades, the consumption of fructose-rich drinks has gained increased attention in relation to the overproduction of uric acid as a byproduct of fructose metabolism.[32] Our found that acute intake of fructose-containing foods such as apples, honey, and fructose powder induced a significant increase in SUA concentration in all participants, regardless of the source of fructose. This finding is consistent with that of a previous study, which indicated that the consumption of apples and apple juice containing fructose increased the SUA concentration in an American

population;[29] in that study, the amount of fructose consumed (26.5 g) was similar to that consumed in our study (25 g). Fructose is a monosaccharide, with a metabolic pathway in the human body that differs greatly from that of glucose, although it is an isomer of glucose. During glucose metabolism, hexokinase catalyzes glucose into glucose-6-phosphate, which then modulates the activity of hexokinase via negative feedback, thereby preventing the overproduction of glucose metabolites. However, fructose metabolism lacks this negative feedback mechanism. When a large amount of fructose was consumed, its rapid metabolism led to the breakdown of adenosine triphosphate (ATP) and phosphate to generate adenosine diphosphate and adenosine monophosphate (AMP). The rapid decrease in phosphate stimulates the production of AMP deaminase, which in turn catalyzes the transformation of AMP to hypoxanthine nucleotide and ultimately to uric acid.[33] The intracellular concentration of uric acid increased and was released into the circulation; as a result, the SUA concentration peaked at 15 min to 1 h after ingestion.[34] Animal and human studies revealed that increase in the SUA concentrations mediated the adverse effects of fructose ingestion in our body's metabolism.[35,36] A previous clinical trial showed that consumption of fructose-containing beverages for 10 weeks significantly elevated the postprandial SUA concentration compared with isocaloric intake of glucose.[37] The ratio of fructose to glucose (F:G) in beverages has a great influence on SUA concentration; that is, consumption of a large amount of fructose increases the SUA concentration. A previous study conducted in male participants showed that an F80:G20 drink induced a higher serum concentration of uric acid than a G50:F50 drink.[38] Therefore, it is necessary to limit the ordinary intake of fructose in soft drinks to maintain health. Some scholars even warned that gouty participants should avoid consuming fruits.[39]

Our data demonstrated that the ingestion of pure fructose rapidly increased the uric acid concentration and resulted in the highest uric acid 2h-AUC; moreover, the 2h-AUC of SUA after apple intake was the lowest among the three dietary treatments. Fruits are enriched with bioactive compounds such as vitamin C and polyphenol, and robust epidemiological evidence showed the beneficial effects of fruit consumption on health.[40] The slow response of the human body to apple intake may be related to its plentiful bioactive substances, including fiber, vitamin C, and antioxidants such as polyphenols.[34,38,41] Polyphenols were found to interfere with intestinal sugar transporters, and result in glucose and fructose absorption.[42] Fibers derived from natural fruits can slow down the digestion of fructose in the small intestine,[43] while vitamin C enhances the urinary urate excretion.[44] We initially proposed the definition of uric acid index and pointed out that it is more optimal for the general population and gouty patients to choose foods based on the uric acid index rather than completely eradicating fruits from their diet. In our study, honey also induced a slow increase in the SUA concentration like apple; in contrast to pure fructose, the slow increase in the SUA concentration may be associated with the presence of phenols in honey, which may impede the intestinal sugar transporters. Our data showed that the uric acid index of honey is higher than that of apple, suggesting that apples may be safer for gouty participants to consume than honey.

Moreover, men exhibited a more rapid increase in the SUA concentration after fructose consumption than women, and the SUA concentration of men did not return to baseline at 120 min. By contrast, the SUA concentration of women returned to baseline by 120 min. The incidence of hyperuricemia and gout in men was four times higher than that in women.[45] Postmenopausal women who did not undergo hormone replacement therapy had high concentrations of SUA;[46] meanwhile, exogenous estrogen intervention decreased the SUA concentrations in postmenopausal women. An epidemiological study in Taiwan conducted in 5,896 participants (2,960 women and 2,936 men) reported that the SUA concentration in women increased with age.[47] The abovementioned studies suggested that estrogen has a positive effect on uric acid metabolism. Moreover, women had stronger capacity to handle the load of dietary fructose. However, there are some limitations in this study. First, this study included healthy young adults, and the response of individuals with gout or compromised kidney function remains unclear. Second, this was a short-term trial; hence, long-term intervention trials are warranted to assess the health effect of fructose from different sources. Finally, due to financial and logistical constraints, two trials were carried out in two groups of participants; however, the serum uric acid responses of these healthy young adults to the same amount of fructose were similar, which strengthens the generalizability of our results.

Conclusion

This study was the first to demonstrate that the consumption of the same amount of fructose derived from different food sources triggered the elevation of SUA concentration to different extents as shown in Figure 4, exhibiting the trend of fructose powder > honey > apple. A gender difference was found in the metabolism of fructose; the SUA concentration of men exhibited a more rapid increase after fructose consumption compared with that of women. Hence, it is meaningful to establish fructose intake limits by gender. Uric acid index may be a useful tool to guide hyperuricemia or gout patients in choosing appropriate foods that they can consume.

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AUTHOR DISCLOSURES

The authors declare no conflicts of interest.

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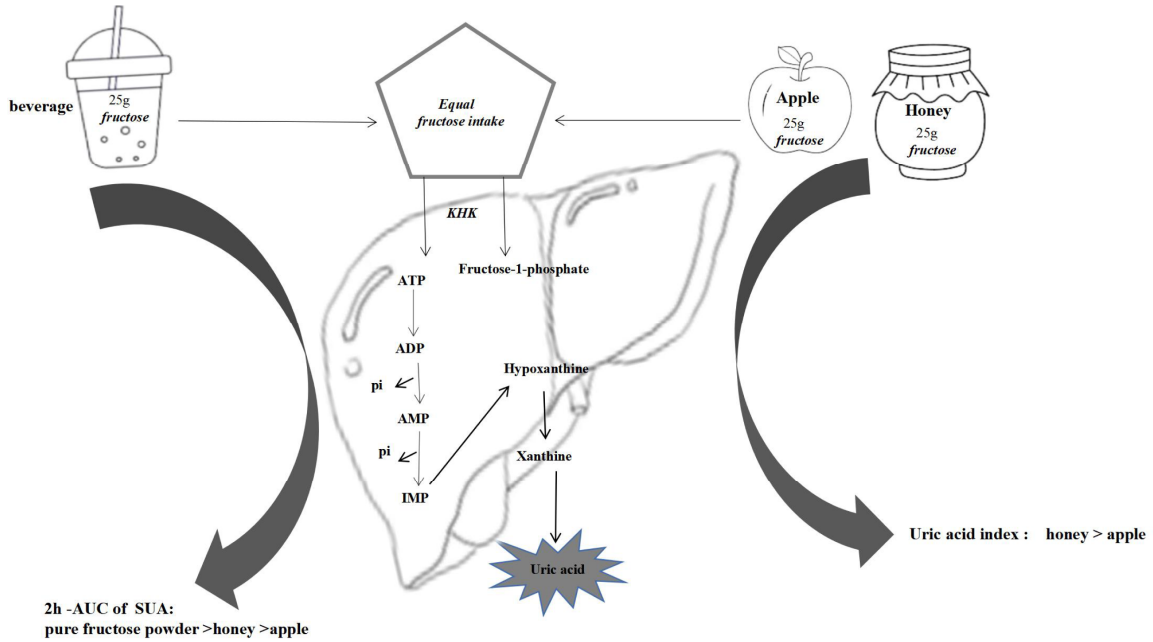

Figure 4. Conceptual diagram of various sources of fructose caused an elevation of serum uric acid concentration to different extent. Fructose readily absorbed can be rapidly metabolized by fructokinase in liver to produce fructose-1-phosphate, leading to a depletion in intracellular ATP and generation of IMP. Then IMP is further degraded to hypoxanthine and xanthine, that is used by xanthine oxidase to generate end-product uric acid. Abbreviations: KHK, ketohexokinase; ATP, adenosine triphosphate; ADP, adenosine diphosphate; AMP, adenosine monophosphate; SUA, serum uric acid; AUC, the areas under the curve.

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