Acute effect of fructose, sucrose, and isomaltulose on uric acid metabolism in healthy participants

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Fructose is associated with hyperuricemia and gout development. Focusing on fructose and fructose-containing disaccharides, we investigated the effects of three different types of carbohydrates (fructose, sucrose, and isomaltulose) on uric acid metabolism and gene expression profiling in peripheral white blood cells. In a randomized crossover study, ten healthy participants ingested test drinks of fructose, sucrose, and isomaltulose, each containing 25 g of fructose. Plasma glucose, serum and urine uric acid, and xanthine/hypoxanthine concentrations were measured. Microarray analysis in peripheral white blood cells and real-time reverse transcription polymerase chain reaction were examined at 0 and 120 in after the intake of test drinks. Serum uric acid concentrations for group fructose were significantly higher than group sucrose at 30–120 min and were significantly higher than those for group isomaltulose at 30–240 min. Several genes involved in the "nuclear factor-kappa B signaling pathway" were markedly changed in group fructose. No significant differences in the mRNA expression levels of tumor necrosis factor, nuclear factor-kappa B, interleukin-1β, and interleukin-18 were noted. This study indicated that fructose intake (monosaccharide) elevated serum uric acid concentrations compared with disaccharide intake. Differences in the quality of carbohydrates might reduce the rapid increase of postprandial serum uric acid concentrations.

Key Words: fructose, isomaltulose, uric acid, postprandial state, gene expression

Fructose has been associated with hyperuricemia and gout development.[1–3] Fructose is metabolized differently from other carbohydrates, and the hepatic metabolism of fructose leads to rapid adenosine triphosphate (ATP) depletion, resulting in uric acid (UA) production.[4] Furthermore, fructose consumption increases blood lactate concentration,[5] interfering with urinary UA excretion.[6] Through these mechanisms, previous studies reported that fructose intake acutely increased serum UA concentrations[7,8] and that sucrose, which is a disaccharide made up of fructose and glucose, also increased plasma UA concentrations.[9] In addition, octacosanol, which is a long-chain aliphatic saturated alcohol, decreased serum UA concentrations.[10] However, whether isomaltulose, which is the structural isomers of sucrose found in honey,[11,12] affects serum concentration and urinary excretion of UA, is still uncertain.

Isomaltulose, which is slowly hydrolyzed in the small intestine compared with sucrose,[13] has been reported to help maintain glycemic control by reducing postprandial plasma glucose and insulin concentrations.[14] In addition, previous study[15] has reported that isomaltulose intake resulted in lower gene expression level of tumor necrosis factor (TNF), a proinflammatory cytokine, in mice. Conversely, the hepatic suppression of endogenous glucose production during the euglycemic-hyperinsulinemic clamp was reduced after a 6-week intervention with fructose ingestion (80 g/day) compared with similar amounts of glucose in healthy young men,[16] and fructose intake for 10 weeks led to increases in the levels of monocyte chemoattractant protein-1 and plasminogen activator inhibitor-1 in overweight/obese men and women.[17] Thus, fructose and isomaltulose may exhibit different effects on the inflammatory response. Since hyperuricemia is associated with the inflammatory response,[18] isomaltulose, which demonstrates an anti-inflammatory effect, may be effective in preventing hyperuricemia.

A genome-wide gene expression analysis (transcriptomics) allows for investigating the comprehensive effects of nutrients in human nutrition intervention studies. Blood is the readily accessible cellular material in human intervention studies. In previous studies, gene expression profiling in white blood cells (WBCs) can reflect food-related metabolic changes in the postprandial state.[19–21] Therefore, gene expression profiling may be useful to examine the effects of different types of carbohydrate intake on UA metabolism in human intervention studies.

Focusing on fructose and fructose-containing disaccharides, this study aimed to elucidate the effects of three different types of carbohydrates on UA metabolism and gene expression profiling in peripheral WBCs.

Materials and Methods

Participants. Ten healthy men were recruited in this study. The participants presented with no history of diabetes and hyperuricemia or gout and did not receive treatment. The participants with hemoglobin A1c (HbA1c) ≥6.5% or fasting blood glucose ≥126 mg/dl were excluded. Other exclusion criteria were those presenting with allergies to food (fructose, sucrose, and isomaltulose) and smoker. The clinical and biological characteristics of the participants are shown in Table 1. The mean values ± SD of age and body mass index was 22.8 ± 0.6 years and 21.9 ± 3.0 g/m², respectively.

This study was conducted following approval by the Ethics Committee of the University of Shizuoka and registered with the University Hospital Medical Information Network (registration number: UMIN000047117). Written informed consent was obtained from all participants before participation in this study. The study was conducted in accordance with the principles of the Helsinki Declaration.

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Table 1. Baseline characteristics of participants

Characteristics	(n = 10)
Age (years)	22.8 ± 0.6
Height (cm)	170.3 ± 9.1
Body weight (kg)	63.3 ± 8.2
Body mass index (kg/m²)	21.9 ± 3.0
Fasting plasma glucose (mg/dl)	95.9 ± 3.8
Hemoglobin A1c (%)	5.1 ± 0.2
Serum uric acid (mg/dl)	6.2 ± 0.8
Serum creatinine (mg/dl)	0.87 ± 0.11
eGFR (ml/min/1.73 m²)	94.3 ± 13.8

eGFR, estimated glomerular filtration rate. Values are presented as mean ± SD.

Study protocol. We used a randomized crossover study design. The experiment was conducted such that the test days were separated by a washout period of at least 7 days. All the participants were asked to avoid heavy exercises and any intake of alcohol and purine-rich foods (>200 mg/100 g) for 3 days before each study day. Furthermore, all the participants were instructed to eat and drink the same prescribed foods during 19:00–20:00 before a test day. After an overnight fast, the participants were provided with their test drinks at 09:00. Subsequently, they were required to ingest 100 ml water; they were required to consume each test drink and water within 10 min. During the experimental period, all the participants were instructed to drink water at 100 ml/h. They underwent a 4 h urine collection from 09:00 to 13:00. Venous blood samples were collected at 0 (i.e., immediately before) and 30, 60, 120, and 240 min after the drink and used for blood analysis; the blood samples at 0 and 120 min were also used for microarray analysis and real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR).

Test drinks. The three different test drinks used were as follows: fructose (F), sucrose (S), and isomaltulose (I). All test drinks contained 25 g fructose and were made up in soda water to produce a 250 ml final total volume. S and I each contained 50 g of available carbohydrate.

Blood and urine analysis methods and anthropometric measurements. Except for the blood used for DNA microarray analysis and qRT-PCR, blood samples were centrifuged at 2,400 rpm for 10 min at 4°C and subsequently separated into plasma or serum and stored at −80°C until the analysis of plasma glucose and serum creatinine (Cre), UA, and xanthine/hypoxanthine (Xa/HX) concentrations. Urine samples were used for the analysis of Cre, UA, and Xa/HX concentrations. The analyses of serum and urine samples were performed by a blood test company (SRL Inc., Tokyo, Japan), except for the analyses of serum and urine Xa/HX concentrations, which were measured using the Xa/HX colorimetric assay kit (BioVision, Milpitas, CA). The incremental area under the curve (iAUC) for the plasma glucose and serum UA and Xa/HX concentrations was calculated from 0 to 240 min. We calculated the urinary 4-h UA and Xa/HX excretion using the following formulas:

urinary UA excretion (mg/4 h) =

urinary UA (mg/dl) × [urinary volume (ml)/100]

urinary Xa/HX excretion (mg/4 h) =

[urinary Xa/HX (μg/ml)/1,000] × urinary volume (ml)

Anthropometric measurements were performed using the bioelectrical impedance analysis method (InBody770; InBody Japan, Tokyo, Japan). Height was measured using a YL-65S stadiometer (Yagami, Nagoya, Japan).

RNA preparation. The RNA preparation was implemented following the aforementioned method.[19] The collected venous blood was directly poured into PAXgeneTM Blood RNA tubes (Qiagen, Hilden, Germany). After the contents were sufficiently mixed, tubes were allowed to stand overnight at room temperature and stored at −30°C. Total RNA was prepared within 6 months after sampling using a PAXgene Blood RNA kit (Qiagen) according to the manufacturer's protocol and stored at −30°C until analysis. Contaminated DNA was removed using a DNase kit (Qiagen), and the resultant RNA was examined by agarose gel electrophoresis and spectrophotometry.

Microarray processing. Microarray analysis was performed on samples taken at 0 and 120 min after the intake of F. Isolated RNA samples were sent to Takara Bio Inc. (Kusatsu, Japan). Total RNA yield was quantified using a Nanodrop 2000 spectrophotometer (Nanodrop Technologies, Wilmington, DE), and integrity was measured using the Agilent 4200 TapeStation (Agilent Technologies, Palo Alto, CA).

An equal amount (200 ng) of RNA prepared from the participants was mixed. Biotinylated cDNA was prepared from 100 ng of total RNA using the GeneChip WT PLUS Reagent Kit (Thermo Fisher Scientific, Waltham, MA) following the manufacturer's instructions. Following fragmentation, 2 μg of single-stranded cDNA was hybridized for 16 h at 45°C on GeneChip Clariom S Array human (Thermo Fisher Scientific). Arrays were washed and stained in the GeneChip Fluidics Station 450 (Thermo Fisher Scientific). Clariom S array was scanned using the GeneChip Scanner 3000 7G (Thermo Fisher Scientific). Data were analyzed using the Expression Console Software 1.4 (Thermo Fisher Scientific) offered signal space transformation-robust multi-array average for gene-level analysis using Thermo Fisher Scientific default analysis settings.

Data analysis. Data were analyzed using the Transcriptome Analysis Console Software (Thermo Fisher Scientific). The threshold set for up- and downregulated genes was fold change >1.5 from the baseline (0 min) to 120 min. The Database for Annotation, Visualization, and Integrated Discovery (DAVID, http://david.abcc.ncifcrf.gov/) is a gene functional classification implement that accommodates a set of functional annotation tools for investigators to analyze the biological roles of genes and perform the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis of the differentially expressed genes. The count of >2 and $p < 0.05$ were considered as cut-off criteria.

cDNA synthesis. Extracted 1 μg of equivalent RNA, 4 μl 5 × PrimeScript RT Master Mix (Takara Bio Inc.), and RNase-free distilled water (Takara Bio Inc.) were reacted in a 20 μl, and cDNA was synthesized.

qRT-PCR. The expression of each gene was determined using qRT-PCR and analyzed using TB Green® Premix Ex Taq™ II (Takara Bio Inc.) and QuantStudio 1 Real-Time PCR System (Thermo Fisher Scientific). Using the analysis of the melting curve, we confirmed that a single PCR product was obtained. The expression level of each gene was corrected by glyceraldehyde-3-phosphate dehydrogenase (GAPDH). The following primers were used (5'–3'): tggcccaggcagtcagaa (forward) and ggtttgctacaacatgggctaca (reverse) for human TNF, cctggaacc acgcctcta (forward) and ggctcatatggtttcccattta (reverse) for human nuclear factor-kappa B (NF-κB), gccctaaacagatgaagtgctc (forward) and gaaccagcatcttcctcag (reverse) for human interleukin-1 beta (IL-1β), caaggaattgtctcccagtgc (forward) and cagccgctttagcagcca (reverse) for human IL-18, and caaggtcatcca tgacaactttg (forward) and ggccatccacagtcttctgg (reverse) for human GAPDH.

Statistical analysis. All data were presented as mean ± SD. The Shapiro–Wilk statistic was employed to test the normality; parametric and nonparametric analyses were performed for normally and non-normally distributed data, respectively. The

significance of the differences among the groups was analyzed using a repeated measures analysis of variance (ANOVA) or Friedman's repeated measures ANOVA, followed by post hoc Tukey's multiple comparisons test. Probability (p) values <0.05 were considered statistically significant in all analyses. We performed the statistical analyses using SPSS for Windows, release 26 (IBM Corp., Armonk, NY).

Results

Figure 1 shows the profiles for changes from the baseline in plasma glucose and serum UA and Xa/HX concentrations. Group F demonstrated a significantly lower plasma glucose concentration than groups S and I at 30 min ($p<0.01$ vs group S; $p<0.05$ vs group I). The plasma glucose concentration for group S was significantly higher than that for group I at 30 min ($p<0.01$) and significantly lower than that for groups F and I at 120 min ($p<0.01$) (Fig. 1A). Group F demonstrated a significantly lower
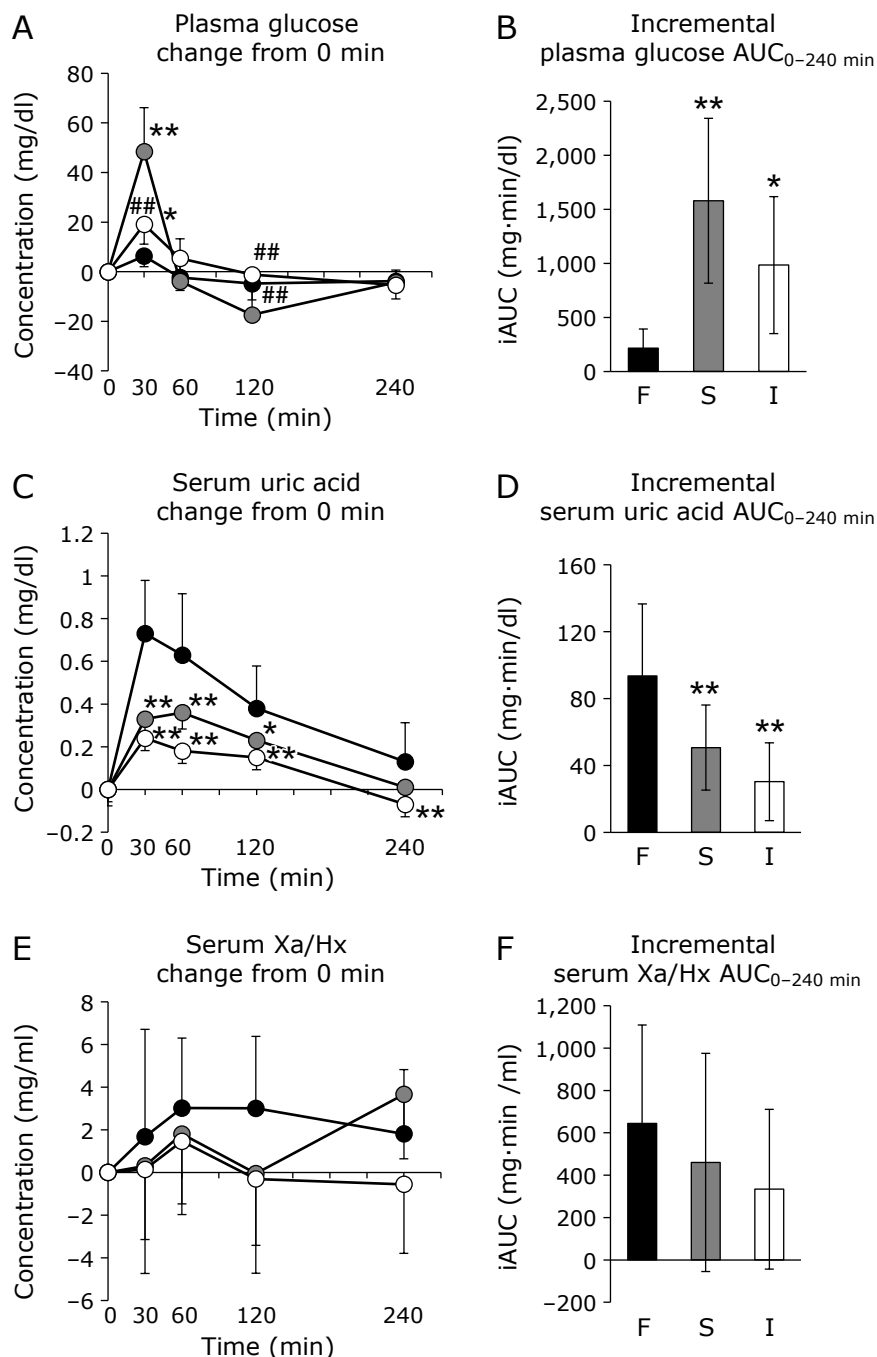

Fig. 1. Changes from 0 min in plasma glucose and serum uric acid and xanthine/hypoxanthine (Xa/Hx) concentrations and incremental plasma glucose and serum uric acid and Xa/Hx area under the curve (AUC) at 0–240 min. Values are presented as mean ± SD. F, fructose; S, sucrose; I, isomaltulose. Black circle and bar, gray circle and bar, and white circle and bar indicate groups F, S, and I, respectively. *,**Significant differences compared with group F (*$p<0.05$, **$p<0.01$). ##Significant differences compared with group S (##$p<0.01$).
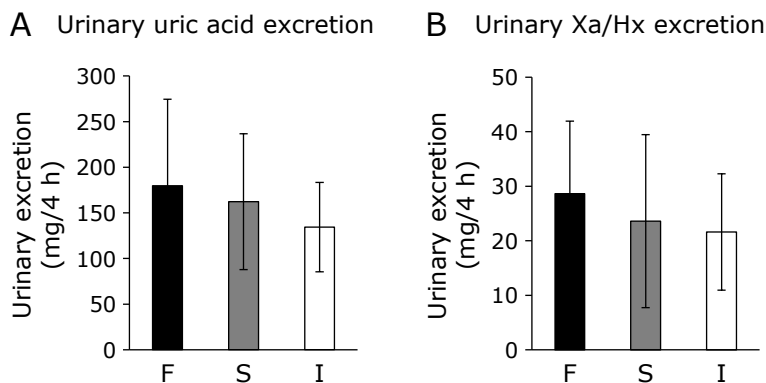
Fig. 2. Urinary uric acid and xanthine/hypoxanthine (Xa/Hx) excretion. Values are presented as mean ± SD. F, fructose; S, sucrose; I, isomaltulose. Black, gray, and white bars indicate groups F, S, and I, respectively.

Table 2. List of KEGG pathways in peripheral WBCs after fructose intake at 120 min

Term	Count	p value
hsa03010:Ribosome	34	<0.001
hsa04612:Antigen processing and presentation	20	0.001
hsa00010:Glycolysis/Gluconeogenesis	18	0.002
hsa01130:Biosynthesis of antibiotics	41	0.002
hsa04064:NF-kappa B signaling pathway	**21**	**0.003**
hsa03008:Ribosome biogenesis in eukaryotes	21	0.003
hsa01200:Carbon metabolism	25	0.003
hsa00051:Fructose and mannose metabolism	10	0.011
hsa00400:Phenylalanine, tyrosine, and tryptophan biosynthesis	4	0.014
hsa03430:Mismatch repair	8	0.015
hsa00030:Pentose phosphate pathway	9	0.018
hsa03013:RNA transport	30	0.035
hsa01220:Degradation of aromatic compounds	3	0.040

KEGG, Kyoto Encyclopedia of Genes and Genomes; WBC, white blood cell.

plasma glucose iAUC$_{0-240 min}$ than groups S and I ($p<0.01$ vs group S; $p<0.05$ vs group I) (Fig. 1B). Serum UA concentrations for group F were significantly higher than those for group S at 30, 60, and 120 min ($p<0.01$ at 30 and 60 min; $p<0.05$ at 120 min) and significantly higher than those for group I at 30, 60, 120, and 240 min ($p<0.01$) (Fig. 1C). Group F demonstrated a significantly higher serum UA iAUC$_{0-240 min}$ than groups S and I ($p<0.01$) (Fig. 1D). No significant differences were observed in serum Xa/HX concentration and iAUC$_{0-240 min}$ among groups (Fig. 1E and F). To compare the differences in urinary excretion among groups, urinary UA and Xa/HX excretion are shown in Fig. 2. No significant differences were observed in urinary UA and Xa/HX excretion (Fig. 2A and B).

A total of 2,348 differentially expressed genes were detected in group F at 120 min, including 1,386 and 962 upregulated and downregulated genes, respectively. The top 10 up- and down-regulated genes are shown in Supplemental Table 1*. The functions of up- and downregulated genes were evaluated using DAVID, and the KEGG pathway analysis was performed. The list of significant pathways is presented in Table 2. Among the significant pathways, our particular focus was on the "NF-κB signaling pathway" (count 21, $p = 0.003$). To confirm the results of the microarray data and observe whether gene expression profiling was affected by any differences in serum UA concentrations after the intake of test drinks, qRT-PCR was performed

(Fig. 3). We selected the four genes, which were involved in the "NF-κB signaling pathway." No significant differences in the mRNA expression levels of TNF, NF-κB, IL-1β, and IL-18 were noted.

Discussion

Glucose transporter (GLUT) 2 and GLUT5 are the main fructose transporters,[22] and GLUT5 appears to be highly specific for fructose.[23] Disaccharides require enzymatic digestion before absorption. In contrast, fructose is a monosaccharide and does not require enzymatic digestion. In this study, groups S and I (disaccharides) demonstrated significantly lower serum UA concentrations than group F (Fig. 1C and D) despite each test drink containing 25 g fructose. Therefore, our results suggest that the rapid fructose absorption via GLUT2 and GLUT5, especially in group F, promoted the hepatic metabolism of fructose, resulting in the increased UA production.

Serum UA concentrations at 30–240 min and serum UA iAUC$_{0-240 min}$ for the group I tended to be lower than those for group S (Fig. 1C and D). Although a previous study reported that monosaccharide ingestion caused rapid trafficking of GLUT2 to the apical membrane in mice,[24] the digestion and absorption rate of isomaltulose was slow at approximately one-fifth that of sucrose.[25] Thus, isomaltulose may suppress the transfer of GLUT2 to the apical membrane owing to the slower digestion rate than that of sucrose, thereby suppressing the increase in serum UA concentration.

We speculated that group I demonstrated higher urinary UA excretion than groups F and S; however, no significant differences in urinary UA and Xa/HX excretion were noted among the groups in this study. Lactate, which increases following fructose consumption,[5] reduces the renal excretion of UA by competing for organic anion transporter (OAT) 1 and OAT3 with UA,[6] and accelerates UA reabsorption in the renal epithelial cells via urate anion transporter 1.[26] It was reported that high fructose intake for 6 days decreased renal fractional UA excretion in humans.[27] Conversely, a previous study that evaluated postprandial plasma lactate concentrations after sucrose-sweetened beverage and high-fructose corn syrup-sweetened beverage intake (each soft drink contained 34.6 and 39.2 g of fructose, respectively) reported no differences in postprandial plasma lactate concentrations and no differences between groups.[28] Although we did not measure plasma lactate concentration, we speculated that lactate does not affect urinary UA excretion since fructose intake was 25 g in this study and we only evaluated acute responses.

Recent studies suggested that crystalline and soluble urate activates various inflammatory pathways.[18] We showed that group F (monosaccharide) demonstrated significantly higher
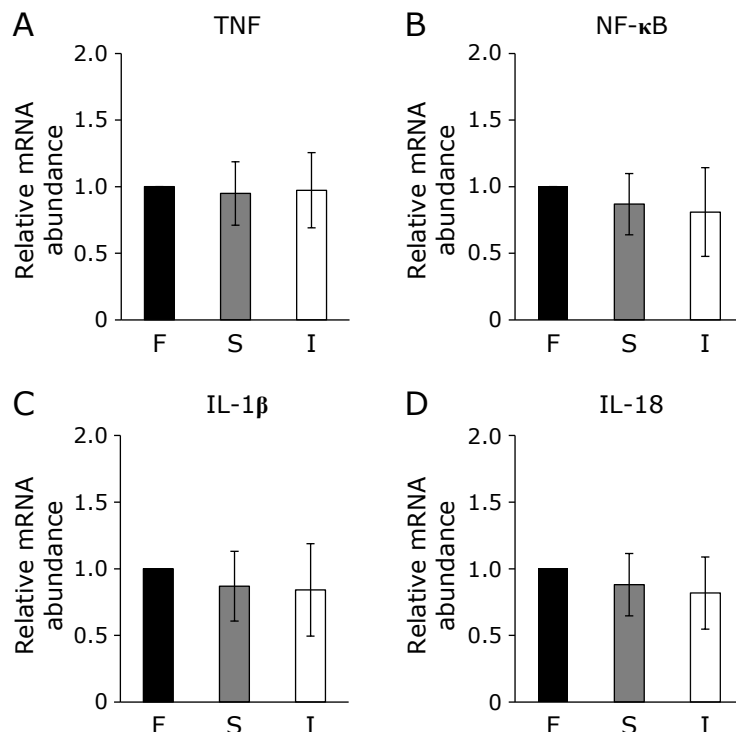
Fig. 3. Peripheral white blood cells' gene expression after the intake of fructose (F), sucrose (S), and isomaltulose (I). Values are presented as mean ± SD. TNF, tumor necrosis factor; NF-κB, nuclear factor-kappa B; IL-1β, interleukin-1 beta; IL-18, interleukin-18. Black, gray, and white bars indicate groups F, S, and I, respectively.

serum UA concentrations than groups S and I (disaccharides) (Fig. 1C and D). Therefore, we speculated that inflammation-related gene expressions would also increase in group F compared with groups S and I. No significant differences were noted in the present study; however, group F tended to show higher NF-κB, IL-1β, and IL-18 mRNA expressions at 120 min than groups S and I (Fig. 3). UA induces renal inflammation via the NF-κB signaling pathway in mice with hyperuricemia,[29] and fructose increases the NF-κB activity because of the decreased transrepression activity of peroxisome proliferator-activated receptor α.[30] Furthermore, acute UA reduction by administrating benzbromarone, which demonstrates a urate-lowering effect, in healthy humans for 2 weeks significantly decreased plasma IL-18 concentrations and decreased TNF and IL-1β secretion in peripheral blood mononuclear cells after 24 h of stimulation.[31] Thus, changes in gene expressions observed in this study may be related to the differences in postprandial serum UA responses. However, we could not observe any significant difference in inflammation-related gene expressions. The reasons may be that the amount of fructose ingested in this study was only 25 g, and only acute responses (2 h after the intake of test drinks) were evaluated. Additionally, UA demonstrates a powerful antioxidant effect,[7,18,32] and the transient postprandial increase in serum UA concentrations observed in this study may contribute to its antioxidant effect.

Several studies focused on the role of intestine in the regulation of serum UA concentrations. Previous study reported that one-third of UA is excreted by the intestine, and that decreased extra-renal urate excretion caused by ATP-binding cassette transporter, sub-family G, member 2 (ABCG2, a high-capacity urate exporter) dysfunction is a common mechanism of hyperuricemia.[33] In addition, recent study suggested that hyperuricemia was characterized by dysregulated intestinal immunity, compromised intestinal barrier, and systemic inflammation.[34] Although we evaluated urinary UA excretion as a renal excretion

indicator in the present study, these previous studies suggest the need to also consider the impact on extra-renal urate excretion. To clarify the effects of differences in the quality of carbohydrates on UA metabolism and inflammatory response, future studies should evaluate the effects on both renal and extra-renal excretion in hyperuricemic animals.

This study exhibited several limitations that should be considered. First, previous studies reported that inflammatory responses were induced by blood glucose fluctuations.[35,36] Therefore, we could not conclude that the changes in inflammation-related gene expressions observed in this study were solely influenced by serum UA concentration fluctuations. Second, we could not evaluate whether the effects on UA metabolism were different when consumed as monosaccharides (glucose and fructose) or disaccharides (sucrose); therefore, this requires further investigation in the future. Third, we did not measure the plasma fructose concentration. A previous study detected plasma fructose concentrations as early as 15 min, reaching maximum concentrations by 2 after high-fructose corn syrup consumption,[28] thereby suggesting that increased plasma fructose concentrations were also observed in this study. Finally, this was a short-term study. A previous report showed that sucrose-sweetened soft drink consumption increased plasma UA concentrations after a 6-month intervention.[37] Therefore, future long-term studies should be conducted to evaluate the effects of different types of carbohydrates on UA metabolism.

This study showed that the intake of fructose (monosaccharide) increased serum UA concentrations compared with disaccharide intake and indicated that differences in the quality of carbohydrates might reduce the rapid increase of the postprandial serum UA concentration.

Author Contributions

The authors' contributions to manuscript were as follows: YK

and HA conceived the research idea and designed the study. YK, MM, AY, and MS collected, analyzed, and interpreted the data. YK wrote the manuscript. TH contributed significant advice. HA edited the manuscript. All the authors contributed to the manuscript revisions and reviewed the final version.

Acknowledgments

Abbreviations

ANOVA	analysis of variance
ATP	adenosine triphosphate
Cre	creatinine
F	fructose
GAPDH	glyceraldehyde-3-phosphate dehydrogenase
GLUT	glucose transporter
HbA1c	hemoglobin A1c
I	isomaltulose
iAUC	incremental area under the curve
IL-1β	interleukin-1 beta
KEGG	Kyoto Encyclopedia of Genes and Genomes
NF-κB	nuclear factor-kappa B
OAT	organic anion transporter
qRT-PCR	real-time quantitative reverse transcription polymerase chain reaction
S	sucrose
TNF	tumor necrosis factor
UA	uric acid
WBC	white blood cell
Xa/HX	xanthine/hypoxanthine

Conflict of Interest

No potential conflicts of interest were disclosed.

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