# Increased Fructose Concentrations in Blood and Urine in Patients With Diabetes

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**OBJECTIVE** — To investigate fructose metabolic changes in patients with diabetes.

**RESEARCH DESIGN AND METHODS** — Serum and urinary fructose concentrations were determined in healthy subjects ($n = 23$) and in nondiabetic ($n = 23$) and diabetic patients ($n = 26$). Fructose was measured using our newly developed method, and $^{13}C_6$-fructose was used as the internal standard. After adding sample to a fixed amount of internal standard, ion-exchange resins and high-performance liquid chromatography pretreatments were performed. Then, the amount of fructose in the sample was measured by gas chromatography–mass spectrometry.

**RESULTS** — Serum fructose concentrations in patients with diabetes (12.0 ± 3.8 μmol/l) were significantly higher than those in healthy subjects (8.1 ± 1.0 μmol/l, $P < 0.001$) and nondiabetic patients (7.7 ± 1.6 μmol/l, $P < 0.001$), and daily urinary fructose excretion was significantly greater in patients with diabetes (127.8 ± 106.7 μmol/day) than in nondiabetic patients (37.7 ± 23.0 μmol/day, $P < 0.001$). In patients with diabetes ($n = 20$), serum fructose concentrations (8.6 ± 1.8 μmol/l, $P < 0.001$) and daily urinary fructose excretion (63.4 ± 63.8 μmol/day, $P < 0.01$) significantly decreased by week 2 after admission.

**CONCLUSIONS** — The present results differed from those of previous studies in that we found that the serum and urinary fructose concentrations decreased rapidly, concomitant with an improvement in glycemia. Therefore, hyperglycemia was associated with increased serum and urinary fructose concentrations in patients with diabetes.

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Fructose is an important dietary source of carbohydrates. In Western countries, daily intake of fructose by adults is ~100 g (1). Due to its unique metabolic properties, fructose promotes adverse metabolic changes, including glucose intolerance (2,3), hyperlipidemia (2,3), and hyperuricemia (4). Moreover, in light of nonenzymatic fructosylation of proteins (5), polyol pathway, and carbonyl stress, fructose is inferred to have an important role in the pathogenesis of diabetic complications. Therefore, if the measurement of serum fructose levels is clinically significant and available as a biomarker, it could be greatly useful. However, previous studies have reported no significant difference in serum fructose concentrations between diabetic and nondiabetic patients (6–8). In these studies, the pretreatment of samples was insufficient to remove glucose, which interfered with the measurement of fructose. In this study, we report serum and urinary fructose concentrations measured by a newly developed method that overcomes this problem of glucose interference, and we describe fructose kinetic changes in patients with diabetes.

## RESEARCH DESIGN AND METHODS

— Three subsets comprised the present study. First, serum fructose concentrations were determined in 23 healthy subjects and in 26 diabetic (diabetes group) and 23 nondiabetic (nondiabetic group) inpatients. Daily urinary fructose excretion was examined in the diabetes group and in the nondiabetic group. Serum fructose concentration, daily urinary fructose excretion, fasting plasma glucose (FPG), $HbA_{1c}$, serum 1,5-anhydroglucitol (1,5-AG), serum creatine, serum triglyceride (TG), serum uric acid (UA) and, daily urinary glucose excretion were determined one time at admission in each diabetic and nondiabetic inpatient. Serum fructose concentration, FPG, $HbA_{1c}$, serum 1,5-AG, serum creatine, serum TG, and serum UA were determined one time in each healthy subject. Second, serum and urine fructose concentrations of 20 patients from the diabetes group were monitored until 2 weeks after admission. Serum fructose concentration, daily urinary fructose excretion, FPG, serum 1,5-AG, serum TG, serum UA, and urinary glucose were determined at admission and week 2 after admission. Third, plasma fructose concentrations were examined at eight time points (immediately before each meal, 2 h after each meal, at 11:00 P.M., and at 3:00 A.M.) for 12 days in 10 hospitalized patients with diabetes. All diabetic and nondiabetic inpatients were recruited at Teikyo University Hospital (Tokyo, Japan), and all healthy subjects were recruited at Tokyo Senbai Hospital. No difference in daily fructose intake was found between diabetic and nondiabetic inpatients. However, in healthy subjects, daily fructose

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**Abbreviations:** 1,5-AG, 1,5-anhydroglucitol; ARI, aldose reductase inhibitor; FPG, fasting plasma glucose; GCMS, gas chromatography–mass spectrometry; HPLC, high-performance liquid chromatography; TG, triglyceride; UA, uric acid.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

intake was not controlled. Informed consent, according to the principles in the Declaration of Helsinki, was obtained from each subject.

### Subjects

In the diabetes group, all patients were hospitalized to undergo standard treatments. Some patients experienced complications arising from diabetes. However, all patients with severe diabetic nephropathy (serum creatine >177 μmol/l) were excluded. The diabetes group was composed of 26 inpatients (13 women, 13 men); the mean age was 52.8 years (range 26–75), and the mean duration of diabetes was 9.5 years (0–22). The mean $HbA_{1c}$ was 10.7% (6.9–16.0), and the mean BMI was 24.7 kg/m$^2$ (15.6–36.7). A total of 5 patients had newly diagnosed diabetes, 2 patients were treated with diet therapy alone, 14 patients received oral hypoglycemic agents, and 5 patients underwent insulin therapy before admission. Of 20 patients from the diabetes group in whom serum and urinary fructose concentrations were monitored until 2 weeks after admission, 2 patients were treated with diet therapy alone, 6 patients were taking oral hypoglycemic agents, and 12 patients underwent insulin therapy during the hospitalization. No patients in the diabetes group were taking aldose reductase inhibitors (ARIs) before admission or during the hospitalization. The nondiabetic group was composed of patients with leukemia, cerebrovascular disease, ischemic heart disease, arrhythmia, pneumonia, lung cancer, peptic ulcer, anorexia nervosa, and sarcoidosis. All patients with renal dysfunction (serum creatine >177 μmol/l) were excluded from the study. It has been reported that patients with liver cirrhosis have much higher plasma fructose levels than normal subjects after oral fructose intake (9). Therefore, patients with liver disease or liver dysfunction (serum aspartate aminotransferase >32 IU or alanine aminotransferase >35 IU) were also excluded. All healthy subjects had undergone physical examination at Tokyo Senbai Hospital, and subjects in whom findings were abnormal were excluded from the study. The eight-point examination (previously described) was performed in four patients treated with diet therapy alone, two patients who were taking oral hypoglycemic agents, and six patients who were undergoing insulin therapy. This group was composed of 10 inpatients (3 women, 7 men); the mean age was 53.5 years (range 26–73), and the mean duration of diabetes was 5.0 years (0–20). The mean $HbA_{1c}$ was 11.2% (8.1–16.4), and the mean BMI was 24.7 kg/m$^2$ (17.6–36.7). All patients were hospitalized to undergo standard treatments, and none of them were taking ARI. Some patients had complications arising from diabetes, but none were considered severe.

### Sampling

Unless otherwise noted, blood samples were obtained from the patients after they had fasted for 12 h. Serum and plasma were separated by centrifugation immediately after collection and stored at −30°C until assayed. A 24-h urine specimen was collected from each patient beginning at 7.00 A.M. Sodium benzoate 5 g was added as a preservative, and the specimen was refrigerated until assayed. The serum sample was obtained just after collection of the 24-h urine sample.

### Determination of fructose contained in samples

We developed a new fructose measurement technique based on Kametani's analytical method of 1,5-anhydrofructose (10). Serum, plasma, and urinary fructose concentrations were measured by gas chromatography–mass spectrometry (GCMS). The internal standard was $^{13}C_6$-fructose (Nippon Sanso, Tokyo, Japan). Samples (100 μl) were added to a fixed amount of internal standard (20 μl). After vortexing, the mixture was applied onto a two-layer column containing, from the bottom, the acetate form (250 μl) of the anion exchanger (AG1-X8; Bio-Rad, Richmond, CA) and the H form (250 μl) of the cation exchanger (AG50W-X8; Bio-Rad). Then, the column was washed with 1 ml distilled water and the eluate was completely collected and evaporated with a centrifugal evaporator (models CC100 and TU040; Tomy, Tokyo, Japan). The dry residue was dissolved in 200 μl acetonitrile-water (80:20) and applied onto a high-performance liquid chromatography (HPLC) system (models L-7100, L-7200, L-7300, L-7490, L-7400, L-5200 and L-7,500; Hitachi, Tokyo, Japan). The HPLC system was fitted with a TSKgel Amido-80 column (Tosoh, Tokyo, Japan) heated at 80°C. The eluent, acetonitrile-water (80:20), was delivered at a flow rate of 0.8 ml/min, and the elution was monitored by a refractive index detector. The peak corresponding to fructose, which was separated clearly from that of glucose, was collected and evaporated. The dry residue was dissolved in 150 μl distilled water containing 2% O-ethylhydroxylamine. The mixture was heated at 110°C for 1 h and was applied onto a reverse-phase HPLC column (Kromasil 100–5C18; Eka Chemicals AB, Bohus, Sweden) heated at 40°C. Distilled water was added to the eluent at a flow rate of 1.0 ml/min, and the elution was monitored by ultraviolet absorbance at 210 nm. Two peaks corresponding to fructose ethyloxime were collected and evaporated. The dry residue was peracetylated for GCMS analysis (models HP6890 and HP5973; Hewlett-Packard, Palo Alto, CA). A gas chromatography column was fitted with a fused silica capillary column (HP-5MS; Hewlett-Packard). The sample was loaded onto the column at 130°C, and the final separation was performed at 250°C. The column was heated 5°C/min from 180°C to 230°C and 20°C/min among the other ranges. Peaks corresponding to fructose in the original sample were observed at $m/z = 271$, whereas peaks corresponding to $^{13}C_6$-fructose were observed at $m/z = 277$. Therefore, the amount of fructose in the original sample was calculated by the area ratio of the peaks of $m/z = 271$ to $m/z = 277$. The coefficient of variance was <3% (intra-assay).

### Determination of serum 1,5-AG and $HbA_{1c}$

Serum 1,5-AG concentration (normal range 78–256 μmol/l) was determined by an established enzymatic method using a 1,5-AG assay clinical test kit (Lana-1,5-AG; Nippon Kayaku, Tokyo, Japan). $HbA_{1c}$ (normal range 4.9–5.9%) was assayed by HPLC (Auto $A_{1c}$; Kyoto Daiichi Kagaku, Kyoto, Japan).

### Statistical analyses

Fructose contained in each sample was measured at least twice. Data are presented as mean ± SD. For normally distributed data, statistical analysis was performed with paired or unpaired Student's *t* test. For any difference in distribution between groups, Wilcoxon's signed-rank test or Welch's unpaired *t* test were performed. Correlations between groups were estimated by Pearson's cor-

**Table 1—*Characteristics of patients determined serum and urinary fructose concentrations***

| | Healthy subjects | Diabetes group | Nondiabetic group |
|---|---|---|---|
| *n* | 23 | 26 | 23 |
| Sex (F/M) | 10/13 | 13/13 | 16/7 |
| Age (years) | 51.4 ± 7.4 | 52.8 ± 14.4 | 63.3 ± 16.3*‡ |
| BMI (kg/m$^2$) | 21.1 ± 2.0 | 24.7 ± 5.6*† | 20.9 ± 4.1 |
| FPG (mmol/l) | 5.06 ± 0.31 | 12.03 ± 4.21*† | 5.16 ± 0.42 |
| $HbA_{1c}$(%) | 5.2 ± 0.3 | 10.7 ± 2.4*† | 5.1 ± 0.4 |
| 1,5-AG (μmol/l) | 138.9 ± 40.6 | 9.4 ± 6.1*† | 134.4 ± 40.6 |
| Urinary glucose (mmol/day) | ND | 164.4 ± 140.6† | 0 |
| Serum creatine (μmol/l) | 61.0 ± 15.9 | 60.1 ± 19.4 | 65.4 ± 17.7 |
| TG (mmol/l) | 0.96 ± 0.35 | 2.08 ± 2.96 | 1.42 ± 1.04 |
| UA (μmol/l) | 297.4 ± 65.4 | 267.7 ± 95.2 | 285.5 ± 59.5 |
| Serum fructose (μmol/l) | 8.1 ± 1.0 | 12.0 ± 3.8§‖ | 7.7 ± 1.6 |
| Urinary fructose (μmol/day) | ND | 127.8 ± 106.7‖ | 37.7 ± 23.0 |

Data are *n* or means ± SD. In all three groups, only one time measurement is shown: "admission" measurements only for the diabetic and nondiabetic patients. *$P < 0.05$ vs. healthy subjects; †$P < 0.05$ vs. nondiabetic group; ‡$P < 0.05$ vs. diabetes group; §$P < 0.001$ vs. healthy subjects; ‖$P < 0.001$ vs. nondiabetic group.

relation coefficient. Statistical significance was set at a *P* value of <0.05.

## RESULTS

### Serum and urine fructose concentrations in patients with diabetes and nondiabetic subjects

As shown in Table 1, serum fructose concentrations in the diabetes group were significantly higher than those in healthy subjects ($P < 0.001$) and the nondiabetic group ($P < 0.001$). Moreover, daily urinary fructose excretion rates in the diabetes group were significantly higher than those in the nondiabetic group ($P < 0.001$).

To determine factors influencing fructose concentrations, correlations between serum or urinary fructose concentrations and indicators were examined (Table 2). Serum fructose concentrations were significantly correlated with FPG ($P < 0.0001$), $HbA_{1c}$ ($P < 0.0001$), 1,5-AG ($P < 0.0001$), and urinary glucose ($P < 0.0001$). Daily urinary fructose excretion rates were significantly correlated with FPG ($P < 0.01$), 1,5-AG ($P < 0.0005$), urinary glucose ($P < 0.0001$), and serum creatine ($P < 0.05$).

### Serial changes over 2 weeks followed in 20 hospitalized patients with diabetes

To determine the influence of glycemic control on serum and urinary fructose concentrations, serial changes in serum and urinary fructose concentrations and glycemic indicators were monitored (Table 3). Serum fructose concentrations significantly decreased by week 2 ($P < 0.001$). Daily urinary fructose excretion significantly decreased by week 2 ($P < 0.01$). Glycemic indicators significantly improved by week 2 ($P < 0.0001$).

### Correlations between fasting plasma fructose concentrations and mean plasma fructose concentrations

To determine whether fasting plasma fructose concentrations correlate with daily mean plasma fructose concentrations, plasma fructose concentrations were measured at eight time points (previously described) for 12 days in 10 hospitalized patients with diabetes. The eight time points covered roughly 1 day. A significant correlation was observed between fasting plasma fructose concentrations and the mean plasma fructose concentrations at all eight time points ($r = 0.883$) (Fig. 1). We confirmed that plasma fructose concentrations were in good agreement with serum fructose concentrations (data not shown).

## CONCLUSIONS

— Fructose is a common monosaccharide that is found naturally in its free form in honey, fruits, and other plants and in a combined form as half of the disaccharide sucrose. When ingested by mouth, fructose is initially absorbed by the small intestine and flows through the liver (1). As a consequence of the high rate of extraction of fructose by liver, correspondingly low fructose concentrations are found in systemic blood vessels after meals (11). Several previous studies have examined serum and urinary fructose concentrations in patients with diabetes. Aloia (6) used gas-liquid chromatography of trimethylsilyl derivatives to measure fructose contained in serum and urine. Pitkänen (7) used gas chromatography/mass fragmentography to measure sugars in the plasma of patients with diabetes. Reductive deuterization of samples and regression analysis of the reduction products were used to calculate concentrations of fructose. Yoshii et al. (8) used GCMS of trimethylsilyl derivatives to measure urinary polyol excretion. However, no increase in serum or urinary fructose concentrations was found in any of the previous studies. The present method overcomes the problems noted below, which are associated with the measurement of fructose, and therefore, we

**Table 2—*Correlations between serum or urinary fructose concentrations and other indicators***

| | Serum fructose (μmol/l) | Urinary fructose (μmol/day) |
|---|---|---|
| *n* | 72 | 49 |
| Age (years) | −0.187 | −0.150 |
| BMI (kg/m$^2$) | 0.200 | −0.041 |
| FPG (mmol/l) | 0.596* | 0.373‡ |
| $HbA_{1c}$ (%) | 0.624* | 0.265 |
| 1,5-AG (μmol/l) | −0.547* | −0.493† |
| Urinary glucose (mmol/day) | 0.545* | 0.671* |
| Serum creatine (μmol/l) | −0.155 | −0.287§ |
| TG (mmol/l) | 0.089 | −0.093 |
| UA (μmol/l) | −0.167 | −0.200 |
| Serum fructose (μmol/l) | | 0.249 |

Data are *n*. Correlations were performed on admission values only. *$P < 0.0001$; †$P < 0.0005$, ‡$P < 0.01$; §$P < 0.05$.

**Table 3—*Serial changes over 2 weeks followed in 20 hospitalized patients (10 women and 10 men) with diabetes***

| | Week 0 | Week 2 | *P* |
|---|---|---|---|
| Serum fructose (μmol/l) | 12.0 ± 3.9 | 8.6 ± 1.8 | <0.0001 |
| Urinary fructose (μmol/day) | 124.5 ± 116.7 | 63.4 ± 63.8 | <0.01 |
| FPG (mmol/l) | 12.3 ± 4.5 | 7.2 ± 2.1 | <0.0001 |
| 1,5-AG (μmol/l) | 8.9 ± 5.0 | 21.1 ± 13.3 | <0.0001 |
| Urinary glucose (mmol/day) | 153.9 ± 119.4 | 33.9 ± 60.0 | <0.0001 |
| TG (mmol/l) | 2.28 ± 3.36 | 1.19 ± 0.57 | <0.05 |
| UA (μmol/l) | 261.7 ± 101.1 | 291.5 ± 107.1 | <0.05 |

Data are means ± SD.

were able to detect small amounts of fructose contained in samples. First, because glucose present in samples interferes with the measurement of fructose in both enzymatic and gas chromatographic analyses, the samples were applied onto a TSKgel Amido-80 column to completely remove all glucose. The pretreatments in previous studies were insufficient to allow for the accurate measurement of small amounts of fructose. Samples were pretreated by glucose oxidase or pyranose oxidase to remove glucose in some studies, whereas in other studies the samples were not subjected to any pretreatment. Second, because complicated pretreatments could impair the precision of measurements, $^{13}C_6$-fructose was used as the internal standard. $^{13}C_6$-fructose and the fructose originally present in samples had equivalent collective and derivative rates in pretreatments, a fact that improved the precision of the measurement. Substrates other than $^{13}C_6$-fructose that were used as the internal standard in previous gas chromatographic analysis studies were α-methyl xyloside and 1-D, 2-$^{13}$C-mannitol (6,7). The internal standard was not described in one enzymatic analysis study.

Serum and urinary fructose concentrations were significantly increased in patients with diabetes in the present study. Although the mean age of the nondiabetic group and the mean BMI of the diabetes group were significantly higher than the corresponding values in the other groups, examination of the influence of age and BMI on serum and urinary fructose concentrations showed no significant correlation. Serum and urinary fructose concentrations decreased rapidly, concomitant with an improvement of glycemia, and therefore, hyperglycemia was associated with increased serum and urinary fructose concentrations in patients with diabetes. We also demonstrated that a single measurement of fasting serum fructose levels is sufficient for monitoring. Although glucose circulates in millimole concentrations, only ~1/1,000 molecules circulates as a free aldehyde and can therefore participate in glycation reactions. Fructose, although circulating in micromole concentrations, is much more reactive in this regard and, therefore, may be comparable to glucose in terms of mediating pathology through nonenzymatic reactions and downstream processes (5,12). We intend to examine changes in serum fructose levels after the treatment of ARI using our newly developed method and evaluate its effects on diabetes complications. It has been reported that fructose promotes hyperlipidemia (2,3) and hyperuricemia (4), and no significant correlation was observed between serum fructose concentration and TG or UA in the present study. However, we only evaluated these factors in the fasting state. We believe further examinations at postprandial periods are needed to evaluate these factors. Moreover, most of these changes were demonstrated in humans or animals that were either on very-high-fructose diets or were receiving fructose intravenously in high doses (2–4), i.e., not on ordinary diets.

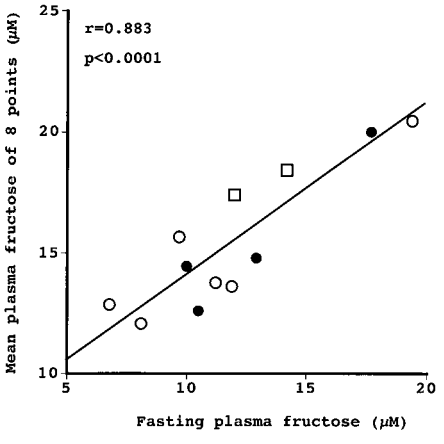


**Figure 1—***Correlation between fasting plasma fructose concentrations and mean plasma fructose concentrations of eight points in patients with diabetes. The eight time points were measured for 12 days in 10 hospitalized patients with diabetes. The examinations were performed in patients treated with diet therapy alone (●), oral hypoglycemic agents (□), and insulin therapy (○).*

Several mechanisms might contribute to the increment of serum and urinary fructose concentrations in patients with diabetes. First, impaired fructose metabolism in the liver might play an important role, given that several studies have shown that the liver metabolizes at least half of all fructose (11,13). Second, the transport system for fructose might be disrupted. Fructose is transported into the liver, at least in part, by the same system as glucose and galactose (14,15). In adipocytes, fructose can enter by at least two different carriers. Hajduch et al. (16) reported that GLUT5 was responsible for mediating ~80% of the total cellular fructose uptake, whereas the remaining 20% was cytochalasin B–sensitive, which most likely reflects transport via GLUT1 and/or GLUT4. Third, the polyol pathway might play a role in the increment of serum and urinary fructose concentrations. This pathway reportedly contributes to increased fructose concentrations in many tissues of patients with diabetes (17) and diabetic animals (18–20). No significant correlation was observed between serum fructose concentrations and daily urinary fructose excretion rates in the present results. When the relation between these two factors was examined in detail, two patterns of urinary fructose excretion were revealed. In one pattern, daily urinary fructose excretion increased in parallel with serum fructose concentration. In the other, fructose excretion remained at a low level while serum fructose increased. A similar relation was revealed between daily urinary fructose and glucose excretion. In one pattern, daily urinary fructose excretion increased in parallel with urinary glucose excretion. In the other, fructose excretion remained at a low level while glucose excretion increased. However, clinical and biochemical differences were not detected between

the groups in the present study. We previously reported in the rat renal tubule the presence of a common reabsorption system of 1,5-AG, fructose and mannose, which was distinct from the major glucose reabsorption system (21). 1,5-AG in the human body originates mainly from foods (4.0–5.5 mg/day) and is metabolically inert (22), whereas fructose is metabolized rapidly in the body. Serum fructose levels increased and serum 1,5-AG levels decreased with progression of hyperglycemia in the present study, indicating that fructose metabolism was impaired as previously described.

In conclusion, serum and urinary fructose concentrations significantly increased in patients with diabetes, and these concentrations decreased rapidly concomitant with an improvement in glycemia.

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