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Study on the Postprandial Blood Glucose Suppression Effect of D-Psicose in Borderline Diabetes and the Safety of Long-Term Ingestion by Normal Human Subjects

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This clinical study was conducted to investigate the safety and effect of D-psicose on postprandial blood glucose levels in adult men and women, including borderline diabetes patients. A randomized double-blind placebo-controlled crossover experiment of single ingestion was conducted on 26 subjects who consumed zero or 5 g of D-psicose in tea with a standard meal. The blood glucose levels at fasting and 30, 60, 90, and 120 min after the meal were compared. The blood glucose level was significantly lower 30 and 60 min after the meal with D-psicose ($p < 0.01$, $p < 0.05$), and a significant decrease was also shown in the area under the curve ($p < 0.01$). The results suggest that D-psicose had an effect to suppress the postprandial blood glucose elevation mainly in borderline diabetes cases. A randomized double-blind placebo-controlled parallel-group experiment of long-term ingestion was conducted on 17 normal subjects who took 5 g of D-psicose or D-glucose with meals three times a day for 12 continuous weeks. Neither any abnormal effects nor clinical problems caused by the continuous ingestion of D-psicose were found.

Key words: D-psicose; sweetener; blood glucose; human; safety

Preventing and improving the metabolic syndromes associated with rapidly increasing dyslipidemia and hyperglycemia are urgent matters to resolve for reducing medical costs that have been rising in recent years. In particular, diabetes tends to accompany such complications as retinopathy, nephropathy and neuropathy; medical costs therefore increase, making it very important to reduce the disease.[1)] Preventing and improving diabetes are based on correcting life-style habits. Above all, it is important to control blood glucose levels after a meal, and a number of studies are in progress to find dietary factors that can suppress blood glucose elevation by using the glycemic index.[2–4)]

D-Psicose (D-ribo-2-hexulose, CAS registration number 551-68-8, molecular formula $C_6H_{12}O_6$, molecular weight 180.156) is a C-3 epimer of D-fructose and is one of the monosaccharides, a rare sugar, that are rarely found in nature. Matsuo *et al.* have clarified the glucose suppression effect of D-psicose by animal experiments. They showed an inhibition capability of α-glucosidase in the suppression mechanism and presumed that the compound had similar behavior to D-fructose in its glucose uptake from liver.[5–7)] Moreover, we have previously conducted a glucose loading experiment on healthy adults using a starch hydrolysate (glucose solution) as the carbohydrate source.[8)] The results showed that approximately 5 g of D-psicose to 75 g of carbohydrate significantly suppressed the blood glucose elevation. Approximately 1 part of D-psicose was effective to 15 parts of carbohydrate ingested. It was also confirmed that a single ingestion of D-psicose had no effect on the blood glucose and insulin levels, meaning that hypoglycemia would not be induced by D-psicose. Those studies showed that D-psicose had an effect of suppressing the postprandial blood glucose elevation. However, from the viewpoint of preventing diabetes, it is important to prove the effect in subjects with impaired glucose tolerance.[9)] This present clinical study was hence conducted to investigate the effect of D-psicose on the postprandial blood glucose level in subjects including borderline diabetes cases.

The safety of D-psicose has already been clarified not to cause mutagenesis nor acute toxicity.[10)] It has also been reported that it was safe to take 0.5–0.6 g/kg of

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Abbreviations: IFG, impaired fasting blood glucose; IGT, impaired glucose tolerance; AUC, area under the curve; BMI, body-mass index; TP, total protein; Alb, albumin; A/G, albumin globulin ratio; T-Bil, total bilirubin; D-Bil, direct bilirubin; I-Bil, indirect bilirubin; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactase dehydrogenase; γ-GTP, γ-glutamyl transpeptidase; CHE, cholinesterase; CPK, creatine phosphokinase; T-Cho, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RLP-C, remnant-like particle cholesterol; TG, triglyceride; FFA, free fatty acid; PL, phospholipids; UN, urea nitrogen; UA, uric acid; Cre, creatinine; Na, sodium; K, potassium; Cl, chlorine; Ca, calcium; P, inorganic phosphate; Mg, magnesium; AMY, serum amylase; GA, glycoalbumin; WBC, white blood cells; RBC, red blood cells; Hb, hemoglobin; Ht, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; PLT, platelet

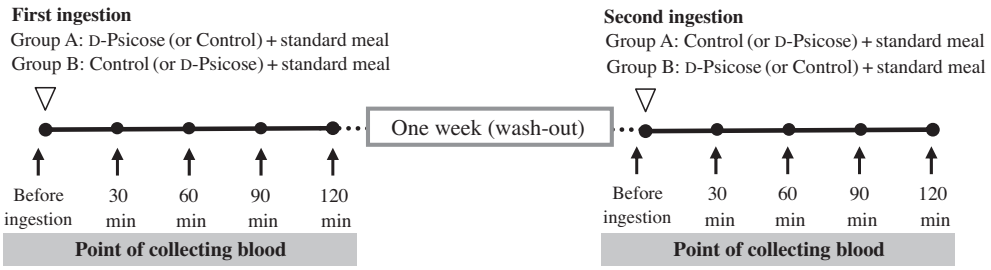

Fig. 1. Outline of the Double-Blind Crossover Study.

body weight of D-psicose as a single dose by a test of the maximum non-effect level to diarrhea in humans.[11] In respect of the metabolism in the human body, 70% of ingested D-psicose is absorbed in the small intestine and excreted in urine without providing any energy. The remaining 30% passed into the feces does not turn into energy.[12–14] It has also been reported that D-psicose, with 70% of the sweetness of sucrose, may already be present in food products coming from fructose during the cooking process.[15,16] Based on these findings for the safety of D-psicose, a further study of the effect on human health by long-term ingestion was medically and biochemically evaluated. Subjects each with a normal blood glucose level consumed 5 g of D-psicose three times a day for 12 weeks.

Materials and Methods

Ethical considerations. All experiments conformed with the Helsinki Declaration (adopted in 1964 and amended in 2004) and were conducted under control by the principal investigator. Exclusion criteria included serious damage to liver and renal functions.

The subjects were given full information about the importance, purpose and contents of the experiment, and provided signed and informed consent that was reviewed and approved by the Ethical Committee of Miyawaki Orthopedic Hospital (meal-loading experiment) and OH Clinic (long-term experiment).

Subjects. The subjects for the meal-loading experiment were recruited by New Drug Development Research Center. More than half of the 30 subjects, being adult men and women, had a fasting blood glucose level of 100–126 mg/dl by a preliminary test, and all the subjects were randomly assigned to two groups so that their fasting blood glucose levels were almost equal in both groups.

The subjects for the long-term experiment on safety were recruited by AIEIsupport. Inclusion criteria were adults whose fasting blood glucose level was below 110 mg/dl and who were not under diabetic care. Eighteen subjects, being men and women, were randomly assigned to two groups so that both groups had similar characteristics regarding the physical examination, blood data, urine data, age and gender.

Materials. The test substance used in this study was 5 g of D-psicose packaged in aluminum foil with over 98% purity. Ten milligram of aspartame (Ajinomoto Co., Tokyo, Japan), whose sweetness is similar to that of D-psicose, was used as the control in the meal-loading experiment. Five gram of D-glucose packaged in aluminum foil was used as the control in the long-term safety experiment.

Methods and schedule. The meal-loading experiment involved a randomized double-blind crossover of a single meal with a one-week washout (Fig. 1). The subjects were randomly assigned to two groups and provided with 200 ml of tea containing either the test or control substance with a standard meal of a bun filled with adzuki bean paste (425 kcal; 84.5 g of carbohydrate, 13.3 g of protein, and 3.7 g of fat). Both the test and control teas were prepared by persons not connected with the experiment. After a one-week interval, the subjects were given another 200 ml of tea with the same standard meal. They had completely finished their meal by 21:00, and then were not allowed to eat or drink until starting normal meals in the following morning. The fasting blood was collected after resting for more than 10 min within 1 h before the meal loading. Each subject consumed the test or control meal for 5 min, and blood was collected 30, 60, 90, and 120 min after the meal.

The long-term safety experiment involved a randomized double-blind parallel-group experiment conducted between August and December 2008 for 18 weeks in total, consisting of a 2-week observation period before starting the treatment, a 12-week treatment period, and 4-week observation period after the treatment (follow-up period). Fasting morning urine and fasting blood were collected at 9:00 after resting for more than 10 min, physical measurements were taken and interviews conducted. These were performed 2 weeks before the treatment, on the first day of the treatment, 2, 4, 8, and 12 weeks after starting the treatment, and 4 weeks after completing the treatment. The subjects were randomly assigned to two groups and took 5 g of either the test or control substance with each meal, three times a day for 12 weeks continuously during the treatment period. The subjects completely finished dinner by 21:00, and were then not allowed to drink anything other than water until the examinations the next morning.

Clinical examination. Meal-loading experiment. The blood glucose level (hexokinase method) and insulin level (chemiluminescent enzyme immuno-assay method) from the blood specimen collected from the antecubital vein in a sitting position were measured. Both measurements were conducted by Daiichi Clinical Laboratories.

Long-term safety experiment. Physical examinations, blood examinations, urine analyses and interviews by the principal investigator were conducted together with the dietary and exercise survey on the examination day. The body weight and percentage of body fat were measured by an HBF-3541T-2 body weight and composition meter (Omron). The body mass index (BMI) was calculated according to the body height measured 2 weeks before starting the experiment. Blood was sampled from the antecubital veins in a sitting position. All the measurements of blood and urine samples were conducted by Kishimoto Clinical Laboratory. Eight parameters formed the basis of the general physical examination: body height, body weight, BMI, body fat percentage, waist circumference, systolic blood pressure, diastolic blood pressure, and pulse rate. The general blood examination comprised 34 parameters: total protein (TP), albumin (Alb), albumin globulin ratio (A/G), total bilirubin (T-Bil), direct bilirubin (D-Bil), indirect bilirubin (I-Bil), alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactase dehydrogenase (LDH), γ-glutamyl transpeptidase (γ-GTP), cholinesterase (CHE), creatine phosphokinase (CPK), total cholesterol (T-Cho), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), remnant-like particle cholesterol (RLP-C), triglyceride (TG), free fatty acid (FFA), phospholipids (PL), urea nitrogen (UN), uric acid (UA), creatinine (Cre), sodium (Na), potassium (K), chlorine (Cl), calcium (Ca), inorganic phosphate (P), magnesium (Mg), serum amylase (AMY), glucose, HbA1c, insulin, glycoalbumin (GA), white blood cells (WBC), red blood cells (RBC), hemoglobin (Hb), hematocrit (Ht), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and platelets (PLT). Five parameters formed the general urine analysis: urine protein, urine glucose, urine urobilinogen, urine specific gravity, and occult blood. A medical

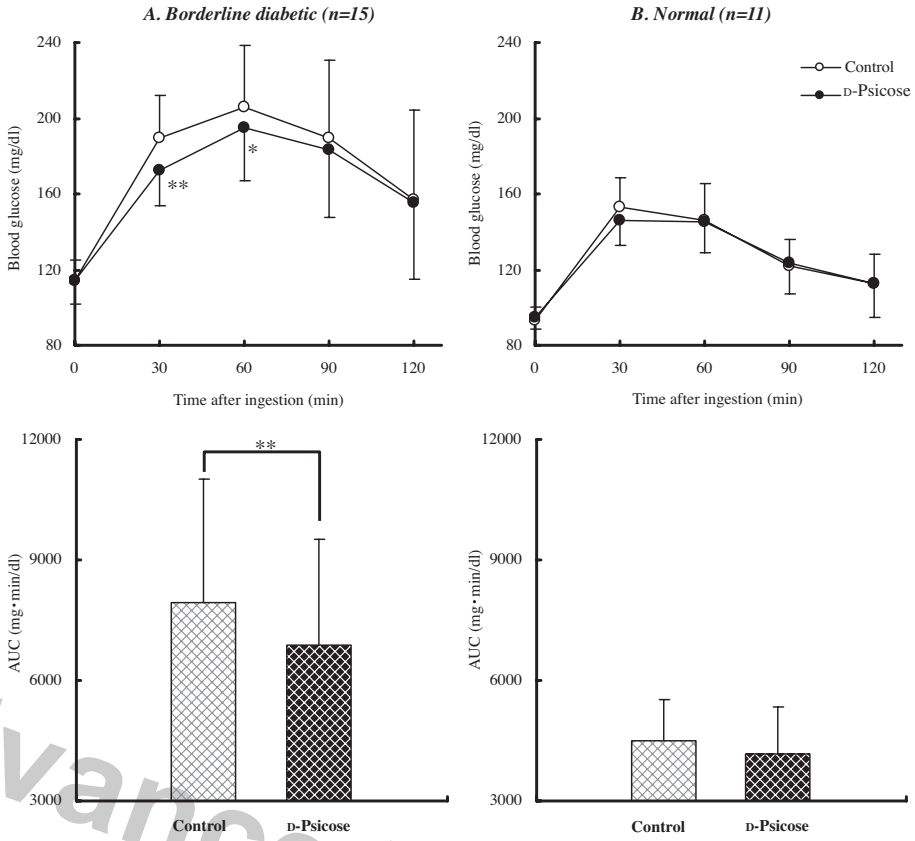

Fig. 2. Effects of D-Psicose on the Blood Glucose Levels (upper panel) and AUC Values (lower panel) after a Meal.
Each value is the mean (±SD). There were significant differences between meals by using a paired *t*-test ($^{*}p < 0.05$, $^{**}p < 0.01$).

doctor interviewed each subject about living habits, abdominal symptoms, defecation condition, occurrence of subjective symptoms in the physical conditions, and adverse events. Each subject recorded every menu and contents of the meals ingested, and the number of steps measured by a pedometer during three days before each examination day. The nutritional components (energy, protein, fat, carbohydrate, cholesterol, and dietary fiber) were calculated by dietitians.

Statistical analyses. Each measured value is expressed as the mean ± standard deviation. The area under the curve (AUC) was calculated by the trapezoidal method, and a paired *t*-test was used for comparing between groups in the meal-loading experiment. An unpaired *t*-test was used for the physical examinations, blood examinations, urine analyses, survey of nutritional components in the diet and degree of exercise to compare the treatment period with the follow-up period between groups in the long-term safety experiment. A multiple-comparison test with Bonferroni correction was used to compare with the data on the first day of the treatment. The software used for the statistical analyses was SPSS version 13.0 J (SPSS Japan), and the level of significance was set at under 5% by a two-sided test.

Results

Meal-loading experiment

Two subjects declared themselves sick due to catching a cold, and another two could not visit the hospital due to their own reasons, these four being excluded from the results. The statistical analysis was accordingly performed on the 26 subjects who had completed the experiment, aged between 22 and 69.

There were 11 subjects in the borderline range, based on the classification and diagnostic criteria for diabetes reported by Japan Diabetes Society in 1999, whose blood glucose levels before and after ingesting the control meal were 110 mg/dl ≤ IFG (impaired fasting blood glucose) < 126 mg/dl or 140 mg/dl ≤ IGT (impaired glucose tolerance at 120 min) < 200 mg/dl, or over 180 mg/dl at 60 min. Another four subjects exceeded the upper limits of IFG and IGT (two over the IFG upper limit at 129 mg/dl and 134 mg/dl, and two over the IGT upper limit at 242 mg/dl and 245 mg/dl) and were considered to have relatively high blood glucose levels. These were analyzed as being in the borderline range for diabetes (Table 1).

Table 1. Characteristics of the Subjects in the Meal-Loading Experiment

	Total (n = 26)	Borderline diabetes (n = 15)	Normal (n = 11)
Age (years old)	55.0 ± 11.4	55.2 ± 11.4	54.7 ± 12.0
Height (cm)	161.8 ± 8.5	162.9 ± 9.8	160.2 ± 6.6
Weight (kg)	65.3 ± 13.1	65.7 ± 11.6	64.8 ± 15.4
BMI	24.9 ± 4.4	24.8 ± 3.9	25.1 ± 5.2
Body fat percentage (%)	28.2 ± 7.8	28.1 ± 7.4	28.4 ± 8.7
Fasting blood glucose (mg/dl)	104.6 ± 13.4	112.5 ± 12.0	93.8 ± 5.0

Each value is mean ± SD.

The average blood glucose levels after meals (upper panel) and AUC (lower panel) are shown in Fig. 2. With all the subjects, the values 30 min and 60 min after the test meal (161.6 ± 21.3 and 173.6 ± 34.2 mg/dl, respectively) were significantly lower ($p < 0.01$ and $p < 0.05$, respectively) than those after the control meal (174.0 ± 26.9 and 180.5 ± 40.4 mg/dl, respectively). The AUC value for the test meal (5738.8 ± 2509.9

mg·min/dl) was significantly less ($p < 0.01$) than the value for the control meal (6482.1 ± 2953.8 mg·min/dl). Similarly, in the sub-group with borderline diabetes, the post-prandial blood glucose levels were significantly lower 30 min and 60 min after the test meal ($p < 0.01$ and $p < 0.05$, respectively), and AUC also significantly lower ($p < 0.01$). On the other hand, no significant differences were found at any time in the blood glucose level and AUC value in the sub-group of normal subjects.

An insulin level 30 min after the test meal (42.1 ± 24.0 μU/ml) was significantly lower ($p < 0.01$) than that after the control meal (48.5 ± 24.5 μU/ml), although no significant difference was found in AUC value between meals (control, 4927.3 ± 2403.4 μU·min/ml; test, 4967.2 ± 2749.7 μU·min/ml) for all subjects. There were no differences in insulin levels and AUC values (control, 4948.4 ± 2765.9 μU·min/ml; test, 4952.6 ± 3083.7 μU·min/ml) in the sub-group with borderline diabetes. There was a significantly lower insulin level found 30 min after the test meal (control, 59.0 ± 24.1 μU/ml; test, 49.2 ± 23.3 μU/ml; $p < 0.05$) in the sub-group of normal subjects, but no differences in AUC values (control, 4898.5 ± 1931.0 μU·min/ml; test, 4987.1 ± 2364.0 μU·min/ml).

Long-term safety experiment

One male subject in the test meal group had a hepatic function indicating a drastic increase from the standard ranges (such as AST 319 IU/l and ALT 332 IU/l) both figures corresponding to Grade 3 of Common Terminology Criteria for Adverse Events, and LDH 481 IU/l after 8 weeks of treatment. This subject was reexamined after 2 weeks of continuous treatment, showing the decreased indicators of AST 33 IU/l, ALT 70 IU/l, and LDH 173 IU/l. This change in the hepatic function was consequently considered to be a transient rise that was not related to the treatment. The subject, however, discontinued participation according to a judgment by the principal doctor of this study. Therefore, the data for 17 subjects aged between 29 and 40 were analyzed. The characteristics of these subjects are shown in Table 2.

No significant differences were apparent between the control and test groups in nutritional intake (energy, protein, fat, carbohydrate, and dietary fiber) and exercise degree during the treatment period.

Changes in the blood biochemical parameters are shown in Table 3. A significant difference in ALT was observed after 8 weeks of treatment ($p < 0.05$), although there were no significant differences in the other parameters between groups. The values for LDH, CHE, TP, Ca, Mg, HDL-C, and GA were considerably lower in the test group than the baseline values and treatment period. AMY was significantly higher. Mg, FFA, and GA values in the control group were significantly lower, and creatinine was significantly higher. Overall, however, those changes were stayed within the standard ranges.

Changes in the hematological parameters are shown in Table 4. No significant difference was apparent in any parameter between groups. There was a significant increase in MCHC observed in the test group when compared between the baseline value and treatment period, although this was within the standard range and time.

Table 2. Characteristics of the Subjects in the Long-Term Safety Experiment

	D-Psicose	Control
Subjects (male/female)	4/4	4/5
Age (years old)	33.4 ± 3.5	34.6 ± 4.0
Height (cm)	166.9 ± 11.2	166.0 ± 9.3
Weight (kg)	59.7 ± 10.8	59.5 ± 10.8
BMI	21.3 ± 2.2	21.5 ± 3.0
Body fat percentage (%)	21.5 ± 5.6	21.2 ± 5.6
Waist circumference (cm)	75.7 ± 6.7	73.7 ± 8.9
Systolic blood pressure (mmHg)	109 ± 16	112 ± 9
Diastolic blood pressure (mmHg)	80 ± 10	75 ± 4
Pulse rate (bpm)	72 ± 15	63 ± 6

Each value is mean ± SD.
There was no significant difference between the groups by the unpaired *t*-test.

The results of the urine analysis are shown in Table 5. A significant difference in specific gravity after 2 weeks of treatment was observed between groups ($p < 0.05$). No abnormality was apparent in urine protein, urine glucose or urine urobilinogen throughout the treatment period. Positive reactions for occult blood were found in one female subject in the test group at 0, 4, and 8 weeks, and in one female subject in the control group at 4, 8, and 12 weeks. However, both of them were in their menstrual period on the examination days and no abnormality was found in renal functions (urea nitrogen and creatinine).

The results of the physical examinations are shown in Table 6. Significant increases were apparent in the control group in body fat percentage and diastolic blood pressure within the standard range in comparison between the baseline values and treatment period. No significant difference was found in the test group.

Table 7 shows the abdominal symptoms and defecation conditions reported during the treatment period. There were two subjects who developed symptoms that could not be unrelated to the treatment. One male subject in the test group had moderate symptoms in the lower digestive tract (diarrhea, borborygmus, and increased defecation frequency) since 4 weeks after starting the treatment, although the relationship is unclear. One female subject in the control group had moderate borborygmus and flatus continuously during the daytime from the beginning until the end of the treatment period, although these symptoms became barely troublesome during the follow-up period (a relationship is recognized).

In respect of other adverse events, two male subjects in the control group showed abnormal changes in the parameters of the clinical examination. These were serious or moderate increases in CPK values from the standard range by the examination 12 weeks after starting the treatment (corresponding to Grade 4 and Grade 2 of Common Terminology Criteria for Adverse Events). It was confirmed that both of them had exercised three days before blood sampling, and those CPK values were back within the normal range in a reexamination after 2 weeks and in an examination during the follow-up period. The event is consequently considered to have been transient.

Table 3. Changes in Blood Biochemical Parameters after the Daily Intake of D-Psicose or Glucose

Item	Standard range	Week 0	Week 2	Week 4	Week 8	Week 12	Follow-up period
ALP (IU/l)							
D-Psicose	101–360	183 ± 53	161 ± 45	163 ± 55	161 ± 50	163 ± 51	185 ± 52
Control		160 ± 41	162 ± 35	166 ± 35	170 ± 42	169 ± 43	176 ± 46
AST (IU/l)							
D-Psicose	10–40	20 ± 3	18 ± 2	18 ± 2	20 ± 3	21 ± 2	19 ± 3
Control		21 ± 8	19 ± 5	21 ± 6	22 ± 5	23 ± 8	21 ± 7
ALT (IU/l)							
D-Psicose	5–45	18 ± 5	15 ± 5	15 ± 4	15 ± 4)*	16 ± 4	16 ± 4
Control		20 ± 8	17 ± 6	19 ± 7	20 ± 6)	21 ± 13	20 ± 9
LDH (IU/l)							
D-Psicose	120–245	188 ± 16	177 ± 12	170 ± 18 **	175 ± 16	173 ± 15	175 ± 14
Control		195 ± 33	188 ± 23	181 ± 21	185 ± 28	196 ± 36	185 ± 30
γ-GTP (IU/l)							
D-Psicose	M: 73≥	24 ± 10	18 ± 7	14 ± 6	15 ± 5	15 ± 7	20 ± 6
Control	F: 35≥	22 ± 7	21 ± 6	20 ± 7	22 ± 7	21 ± 9	23 ± 8
CHE (IU/l)							
D-Psicose	201–513	323 ± 62	302 ± 61*	297 ± 66*	305 ± 65	304 ± 69	323 ± 67
Control		309 ± 76	305 ± 74	309 ± 82	313 ± 85	319 ± 81	323 ± 77
CPK (IU/l)							
D-Psicose	M: 50–230	120 ± 49	115 ± 59	107 ± 43	123 ± 44	120 ± 41	118 ± 54
Control	F: 30–165	147 ± 105	122 ± 50	136 ± 55	165 ± 86	201 ± 222	143 ± 82
AMY (IU/l)							
D-Psicose	42–127	80 ± 19	79 ± 15	84 ± 17	88 ± 20	93 ± 34	92 ± 23*
Control		83 ± 20	91 ± 29	88 ± 19	101 ± 52	91 ± 24	88 ± 21
TP (g/dl)							
D-Psicose	6.5–8.3	7.3 ± 0.5	7.0 ± 0.5*	7.1 ± 0.5	7.2 ± 0.4	7.3 ± 0.4	7.3 ± 0.5
Control		7.2 ± 0.2	7.1 ± 0.3	7.0 ± 0.3	7.2 ± 0.4	7.3 ± 0.3	7.3 ± 0.3
Alb (g/dl)							
D-Psicose	3.7–5.2	4.6 ± 0.2	4.5 ± 0.2	4.5 ± 0.2	4.5 ± 0.1	4.5 ± 0.2	4.5 ± 0.2
Control		4.6 ± 0.2	4.6 ± 0.2	4.5 ± 0.2	4.5 ± 0.2	4.6 ± 0.2	4.6 ± 0.2
A/G							
D-Psicose	1.10–2.00	1.72 ± 0.24	1.79 ± 0.20	1.76 ± 0.18	1.70 ± 0.21	1.63 ± 0.13	1.60 ± 0.18
Control		1.76 ± 0.16	1.79 ± 0.20	1.82 ± 0.20	1.71 ± 0.17	1.70 ± 0.19	1.69 ± 0.17
T-Bil (mg/dl)							
D-Psicose	0.2–1.2	1.2 ± 0.6	1.2 ± 0.6	1.1 ± 0.3	1.1 ± 0.2	1.0 ± 0.3	0.9 ± 0.2
Control		1.2 ± 0.4	1.1 ± 0.3	1.0 ± 0.3	1.1 ± 0.3	1.0 ± 0.3	1.0 ± 0.4
D-Bil (mg/dl)							
D-Psicose	0.1–0.6	0.5 ± 0.3	0.4 ± 0.3	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.3 ± 0.1
Control		0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.3 ± 0.1	0.4 ± 0.2
I-Bil (mg/dl)							
D-Psicose	0.1–0.8	0.7 ± 0.3	0.8 ± 0.3	0.7 ± 0.2	0.7 ± 0.1	0.7 ± 0.2	0.6 ± 0.2
Control		0.8 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2
UN (mg/dl)							
D-Psicose	8.0–20.0	12.4 ± 3.2	12.7 ± 2.4	11.2 ± 3.2	11.5 ± 1.8	12.1 ± 3.9	12.1 ± 4.2
Control		13.3 ± 4.2	11.8 ± 2.8	13.3 ± 3.5	11.9 ± 2.8	12.6 ± 3.3	13.1 ± 2.5
Cre (mg/dl)							
D-Psicose	M: 0.7–1.3	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1
Control	F: 0.4–1.1	0.9 ± 0.1	0.9 ± 0.1	1.0 ± 0.1*	1.0 ± 0.1*	0.9 ± 0.1	0.9 ± 0.1
UA (mg/dl)							
D-Psicose	7.0>	4.4 ± 1.0	4.4 ± 1.0	4.1 ± 0.9	4.5 ± 0.8	4.4 ± 1.1	4.6 ± 1.2
Control		4.4 ± 1.5	4.5 ± 1.6	4.6 ± 1.7	4.7 ± 1.6	4.6 ± 1.6	4.5 ± 1.8
Na (mEq/dl)							
D-Psicose	135–147	140 ± 0	141 ± 1	139 ± 1	140 ± 1	138 ± 2	140 ± 1
Control		139 ± 2	140 ± 1	139 ± 2	139 ± 2	138 ± 1	140 ± 1
K (mEq/dl)							
D-Psicose	3.5–5.0	4.5 ± 0.4	4.3 ± 0.4	4.4 ± 0.4	4.5 ± 0.4	4.4 ± 0.4	4.6 ± 0.3
Control		4.5 ± 0.4	4.4 ± 0.4	4.5 ± 0.4	4.5 ± 0.4	4.4 ± 0.4	4.6 ± 0.4
Cl (mEq/dl)							
D-Psicose	98–108	103 ± 2	104 ± 1	104 ± 2	104 ± 2	101 ± 2	103 ± 2
Control		103 ± 2	103 ± 1	103 ± 1	104 ± 2	102 ± 1	103 ± 2

Table 3. *Continued*

Item	Standard range	Week 0	Week 2	Week 4	Week 8	Week 12	Follow-up period
Ca (mEq/dl)							
D-Psicose	8.4–10.2	9.5 ± 0.5	9.5 ± 0.5	9.2 ± 0.5*	9.5 ± 0.5	9.4 ± 0.5	9.6 ± 0.4
Control		9.5 ± 0.3	9.5 ± 0.4	9.3 ± 0.3	9.4 ± 0.2	9.4 ± 0.3	9.7 ± 0.3
P (mEq/dl)							
D-Psicose	2.5–4.6	3.4 ± 0.2	3.5 ± 0.5	3.4 ± 0.2	3.5 ± 0.5	3.3 ± 0.3	3.5 ± 0.3
Control		3.3 ± 0.3	3.5 ± 0.4	3.5 ± 0.4	3.4 ± 0.3	3.4 ± 0.3	3.4 ± 0.3
Mg (mEq/dl)							
D-Psicose	1.8–2.6	2.5 ± 0.1	2.5 ± 0.1	2.3 ± 0.1**	2.5 ± 0.1	2.5 ± 0.1	2.4 ± 0.1
Control		2.4 ± 0.1	2.5 ± 0.1	2.2 ± 0.1**	2.5 ± 0.1	2.4 ± 0.1	2.3 ± 0.1
T-Cho (mg/dl)							
D-Psicose	130–219	175 ± 22	165 ± 28	169 ± 26	182 ± 30	175 ± 22	178 ± 26
Control		189 ± 47	187 ± 42	187 ± 33	186 ± 40	188 ± 49	191 ± 45
LDL-C (mg/dl)							
D-Psicose	70–139	93 ± 21	98 ± 30	100 ± 24	108 ± 25	100 ± 27	93 ± 23
Control		105 ± 49	106 ± 45	104 ± 33	101 ± 37	105 ± 55	104 ± 48
HDL-C (mg/dl)							
D-Psicose	M: 40–77	64 ± 9	57 ± 10*	56 ± 8*	57 ± 8	59 ± 10	68 ± 7
Control	F: 40–90	69 ± 14	70 ± 18	68 ± 16	69 ± 14	67 ± 13	70 ± 14
TG (mg/dl)							
D-Psicose	40–149	84 ± 40	73 ± 29	77 ± 34	96 ± 40	78 ± 34	85 ± 28
Control		70 ± 36	74 ± 38	78 ± 50	77 ± 49	73 ± 28	71 ± 35
FFA (mg/dl)							
D-Psicose	0.10–0.90	0.62 ± 0.24	0.54 ± 0.18	0.56 ± 0.18	0.48 ± 0.14	0.63 ± 0.20	0.35 ± 0.14
Control		0.71 ± 0.23	0.53 ± 0.20	0.53 ± 0.12	0.63 ± 0.23	0.52 ± 0.15	0.43 ± 0.13*
PL (mg/dl)							
D-Psicose	140–260	194 ± 23	192 ± 25	185 ± 25	202 ± 31	197 ± 16	198 ± 25
Control		209 ± 37	224 ± 39	210 ± 30	210 ± 32	212 ± 29	208 ± 37
RLP-C (mg/dl)							
D-Psicose	75≥	6.2 ± 3.0	5.5 ± 2.1	5.8 ± 2.6	7.1 ± 3.0	5.9 ± 2.5	6.3 ± 2.1
Control		5.7 ± 2.5	5.6 ± 2.8	5.8 ± 3.8	5.8 ± 3.7	5.5 ± 2.0	5.3 ± 2.6
Glucose (mg/dl)							
D-Psicose	70–109	92 ± 4	94 ± 4	95 ± 4	95 ± 6	89 ± 5	93 ± 9
Control		92 ± 6	91 ± 8	92 ± 7	94 ± 7	90 ± 8	95 ± 8
HbA1c							
D-Psicose	4.3–5.8	4.7 ± 0.2	4.7 ± 0.2	4.8 ± 0.2	4.7 ± 0.3	4.7 ± 0.2	4.8 ± 0.2
Control		4.6 ± 0.2	4.6 ± 0.2	4.7 ± 0.2	4.6 ± 0.2	4.6 ± 0.2	4.6 ± 0.2
Insulin (μU/ml)							
D-Psicose	4.4–15.4	8.0 ± 0.6	7.9 ± 0.7	8.4 ± 0.5	7.9 ± 0.8	7.5 ± 0.7	8.7 ± 0.5
Control		8.1 ± 0.9	7.6 ± 0.8	8.4 ± 1.1	7.8 ± 0.9	7.4 ± 1.3	8.4 ± 1.0
GA (%)							
D-Psicose	12.4–16.3	15.1 ± 1.0	14.9 ± 0.8	15.2 ± 0.9	15.0 ± 0.8	14.6 ± 0.8	14.3 ± 0.7*
Control		15.3 ± 1.1	15.1 ± 1.0	15.4 ± 1.0	15.0 ± 0.8	14.7 ± 1.0	4.2 ± 0.8**

Each value is mean ± SD. M, male; F, female.
There were significant differences from the week 0 value, as determined by the Bonferroni method ($^{*}p < 0.05$, $^{**}p < 0.01$).
There was a significant difference between the groups by the unpaired *t*-test ($^{\#}p < 0.05$).

Discussion

The adult male and female subjects in the current study, including those with borderline diabetes, ingested 5 g of individually packaged D-psicose as a sweetener with a standard meal, and we investigated the postprandial glucose suppression effect of D-psicose. The results reveal that D-psicose significantly suppressed the blood glucose level when compared with the control. A more remarkable suppressive effect was apparent with the borderline diabetes cases in a stratified analysis between the sub-groups for borderline diabetes and normal health. This result indicates D-psicose to have had a better postprandial glucose suppression effect in borderline diabetes cases than in normal healthy subjects.

We also conducted in this study an experiment using common meals (a mixed diet) which was substantially different from the previous study using a glucose solution with healthy humans. It had been reported that the postprandial blood glucose level would be elevated more slowly after food ingestion than after the ingestion of a glucose solution due to the delay in digestion and absorption velocity (a lower glycemic index).[2,17,18]

On the other hand, fructose, the same ketose as that in D-psicose, had been found to have a suppressive effect on the postprandial blood glucose elevation, and the absorption rate of fructose reportedly rose under the condition in which free glucose coexisted.[19–22] It would thus take time to generate free glucose by digestion when starchy food is used as the carbohydrate source,

Table 4. Changes in Hematological Parameters after the Daily Intake of D-Psicose or Glucose

Item	Standard range	Week 0	Week 2	Week 4	Week 8	Week 12	Follow-up period
WBC ($10^3/\mu l$)							
D-Psicose	3.3–9.0	4.4 ± 1.2	4.8 ± 1.1	4.2 ± 0.6	4.6 ± 0.8	4.9 ± 1.0	4.4 ± 0.8
Control		5.0 ± 1.3	5.2 ± 1.5	5.1 ± 1.2	5.4 ± 1.3	5.5 ± 1.3	4.8 ± 1.3
RBC ($10^4/\mu l$)							
D-Psicose	M: 430–570	457 ± 26	444 ± 34	446 ± 32	463 ± 27	458 ± 27	465 ± 30
Control	F: 380–500	456 ± 49	461 ± 55	458 ± 57	465 ± 52	463 ± 51	467 ± 52
Hb (g/dl)							
D-Psicose	M: 13.5–17.6	13.6 ± 1.3	13.6 ± 1.4	13.3 ± 1.4	13.9 ± 1.4	13.7 ± 1.4	14.0 ± 1.5
Control	F: 11.3–15.2	13.3 ± 1.6	13.9 ± 1.5*	13.5 ± 1.7	13.8 ± 1.7	13.7 ± 1.5	13.9 ± 1.7
Ht (%)							
D-Psicose	M: 40.0–52.0	42.1 ± 3.4	40.7 ± 4.0	40.9 ± 3.9	42.6 ± 3.7	42.0 ± 3.7	42.9 ± 4.0
Control	F: 34.0–46.0	41.1 ± 3.8	41.5 ± 4.2	41.2 ± 4.1	42.1 ± 4.2	41.8 ± 3.9	42.5 ± 4.3
MCV (fl)							
D-Psicose	M: 86–104	92 ± 4	92 ± 4	92 ± 4	92 ± 4	92 ± 4	92 ± 4
Control	F: 82–101	90 ± 3	90 ± 3	90 ± 3	91 ± 4	90 ± 4	91 ± 4
MCH (pg)							
D-Psicose	M: 28.0–34.6	29.8 ± 1.5	30.4 ± 1.3	29.9 ± 1.4	30.0 ± 1.5	30.0 ± 1.6	30.0 ± 1.6
Control	F: 26.3–34.7	29.2 ± 1.0	30.1 ± 1.0	29.5 ± 0.9	29.6 ± 1.0	29.6 ± 1.2	29.7 ± 1.2
MCHC (%)							
D-Psicose	M: 31.0–36.6	32.4 ± 1.0	33.3 ± 0.9*	32.6 ± 0.7	32.6 ± 0.8	32.7 ± 1.0	32.5 ± 0.8
Control	F: 30.0–36.6	32.4 ± 1.1	33.4 ± 0.6	32.7 ± 1.0	32.7 ± 1.1	32.7 ± 0.8	32.5 ± 0.8
PLT ($10^4/\mu l$)							
D-Psicose	12.0–34.0	23.8 ± 5.0	24.4 ± 5.2	22.7 ± 4.7	23.4 ± 4.2	22.2 ± 5.4	25.0 ± 4.1
Control		24.4 ± 5.8	23.8 ± 6.6	23.9 ± 4.5	23.6 ± 4.7	23.8 ± 5.1	24.9 ± 5.7

Each value is mean ± SD. M, male; F, female.
There were significant differences from the week 0 value, as determined by the Bonferroni method (* $p < 0.05$).
There was no significant difference between the groups by the unpaired *t*-test.

Table 5. Changes in Urinary Parameters after the Daily Intake of D-Psicose or Glucose

Item	Standard range	Week 0			Week 2			Week 4			Week 8			Week 12			Follow-up period		
Urine protein		−	±	+	−	±	+	−	±	+	−	±	+	−	±	+	−	±	+
D-Psicose	(−)	8	0	0	8	0	0	8	0	0	8	0	0	8	0	0	8	0	0
Control		9	0	0	9	0	0	9	0	0	9	0	0	9	0	0	9	0	0
Urine glucose		−	±	+	−	±	+	−	±	+	−	±	+	−	±	+	−	±	+
D-Psicose	(−)	8	0	0	8	0	0	8	0	0	8	0	0	8	0	0	8	0	0
Control		9	0	0	9	0	0	9	0	0	9	0	0	9	0	0	9	0	0
Urine urobilinogen		−	±	+	−	±	+	−	±	+	−	±	+	−	±	+	−	±	+
D-Psicose	(±)	0	8	0	0	8	0	0	8	0	0	8	0	0	8	0	0	8	0
Control		0	9	0	0	9	0	0	9	0	0	9	0	0	9	0	0	9	0
Occult blood		−	±	1+	2+	3+	−	±	1+	2+	3+	−	±	1+	2+	3+	−	±	1+	2+	3+	−	±	1+	2+	3+	−	±	1+	2+	3+
D-Psicose	(−)	7	0	1	0	0	8	0	0	0	0	7	0	1	0	0	7	0	0	1	0	8	0	0	0	0	8	0	0	0	0
Control		9	0	0	0	0	9	0	0	0	0	8	0	0	0	1	8	0	1	0	0	8	0	0	1	0	9	0	0	0	0

Item	Standard range	Week 0	Week 2	Week 4	Week 8	Week 12	Follow-up period
Urine specific gravity							
D-Psicose	1.005–	1.024 ± 0.009	1.029 ± 0.007 #	1.022 ± 0.010	1.025 ± 0.008	1.024 ± 0.008	1.021 ± 0.005
Control	1.030	1.021 ± 0.007	1.020 ± 0.006 #	1.021 ± 0.006	1.019 ± 0.006	1.019 ± 0.006	1.021 ± 0.007

urine protein, urine sugar, urobilinogen... Values show the numbers of people. [− negative, ± false-positive, + positive]
occult blood... Values show the numbers of people. [− negative, ± false-positive, 1+ positive (mild), 2+ positive (moderate), 3+ positive (serious)]
urinary specific gravity... Each value is mean ± SD.
There was no significant difference from the week 0 value, as determined by the Bonferroni method.
There was a significant difference between the groups by the unpaired *t*-test (# $p < 0.05$).

and accordingly, a milder suppressive effect of fructose on postprandial blood glucose elevation has reportedly been recognized.[23] Moreover, in the case of the ingestion of glucose and fructose solutions, which is not influenced by the absorption velocity, a postprandial blood glucose suppressive effect has been recognized in healthy humans and in type II diabetes mellitus patients.[7,24] The same effect as that of fructose can be expected with D-psicose. In the experiment with rats using starchy feed conducted by Matsuo, a milder suppressive effect of D-psicose on postprandial blood glucose elevation was actually recognized.[5]

In respect of insulin levels, it has been reported that reduced levels were observed together with postprandial blood glucose suppression in the study on healthy humans.[8] However, no significant differences were

Table 6. Changes in Anthropometric Indicators after the Daily Intake of D-Psicose or Glucose

Item	Week 0	Week 2	Week 4	Week 8	Week 12	Follow-up period
Weight (kg)						
D-Psicose	59.9 ± 11.4	60.0 ± 11.3	60.2 ± 11.5	60.4 ± 11.9	60.0 ± 11.3	60.3 ± 11.7
Control	59.5 ± 10.9	59.9 ± 10.7	59.8 ± 10.1	59.9 ± 10.6	60.0 ± 10.5	60.0 ± 10.3
BMI						
D-Psicose	21.4 ± 2.1	21.5 ± 2.1	21.5 ± 2.2	21.6 ± 2.2	21.5 ± 2.1	21.6 ± 2.1
Control	21.5 ± 3.0	21.6 ± 2.9	21.7 ± 2.8	21.7 ± 2.9	21.7 ± 3.0	21.7 ± 3.0
Body fat percentage (%)						
D-Psicose	21.6 ± 4.6	21.3 ± 4.6	21.3 ± 4.4	21.8 ± 5.0	22.4 ± 3.9	23.2 ± 4.4
Control	21.1 ± 6.1	21.4 ± 5.6	22.5 ± 6.7	22.2 ± 5.6	23.0 ± 5.8*	23.0 ± 6.3**
Waist circumference (cm)						
D-Psicose	75.1 ± 7.4	74.8 ± 7.8	75.0 ± 7.5	74.7 ± 7.4	75.2 ± 6.8	75.4 ± 7.1
Control	72.8 ± 8.8	73.2 ± 9.0	73.3 ± 8.7	73.1 ± 8.9	72.8 ± 8.5	72.4 ± 9.0
Systolic blood pressure (mmHg)						
D-Psicose	106 ± 14	103 ± 10	108 ± 18	104 ± 15	105 ± 13	102 ± 12
Control	107 ± 11	108 ± 10	109 ± 9	109 ± 11	114 ± 8	111 ± 11
Diastolic blood pressure (mmHg)						
D-Psicose	73 ± 10	71 ± 8	67 ± 12	73 ± 6	73 ± 8	73 ± 6
Control	66 ± 8	71 ± 6	74 ± 9	72 ± 6	78 ± 5**	79 ± 11
Pulse (bpm)						
D-Psicose	68 ± 11	72 ± 8	67 ± 13	65 ± 12	65 ± 13	69 ± 7
Control	62 ± 10	64 ± 10	62 ± 9	65 ± 9	62 ± 10	61 ± 12

Each value is mean ± SD.
There were significant differences from the week 0 value, as determined by the Bonferroni method ($^{*}p < 0.05$, $^{**}p < 0.01$).
There was no significant difference between the groups by the unpaired *t*-test.

Table 7. Abdominal Symptoms and Defecation Conditions during the Long-Term Experiments

	D-Psicose (n = 8)		Control (n = 9)	
	no.	%	no.	%
Borborygums	2	25.0	4	44.4
Abdominal wind	5	62.5	5	55.6
Distension	2	25.0	3	33.3
Burp	1	12.5	1	11.1
Loose feces	1	12.5	0	0.0
Hard feces	0	0.0	1	11.1
Incomplete evacuation	1	12.5	1	11.1
Increased frequency of defecation	4	50.0	2	22.2
Decreased frequency of defecation	0	0.0	1	11.1

apparent after 60 min nor in AUC value in present study involving subjects mainly with borderline diabetes. It is presumed that the subjects in present study had a peak insulin secretion approximately twice that of healthy humans, making the feedback to decrease the insulin secretion level from the suppression of blood glucose elevation relatively weak.

Two mechanisms for D-psicose suppressing the elevation of postprandial blood glucose with carbohydrate ingestion are currently presumed. One involves the inhibition of α-glucosidase. α-Glucosidase has been shown by *in vitro* and animal experiments to have an inhibitory function against such digestive enzymes of disaccharides as sucrase and maltase, and that the effect was stronger when sucrose was used as a substance than with maltose.[5,6] L-Arabinose and D-xylose are well known as monosaccharides that inhibit the activity of α-glucosidase. In particular, L-arabinose has been developed as a food product utilizing the function of inhibiting sucrase, and is contained in a sweetening product as a food for specified health use in Japan, with the health claim that it suppresses the postprandial blood glucose elevation.[25] Similar food development could be expected with D-psicose. The other hypothesis is that D-psicose might promote the uptake of glucose and an accumulation of glycogen in the liver which raises the glucose tolerance.

It has been confirmed that D-fructose becomes D-fructose 1-phosphate by the action of fructokinase which promotes the transition of glucokinase from cell nuclei to the cytoplasmic matrix in the liver.[26,27] Phosphorylation of glucose by glucokinase is rate limiting in the metabolism of hepatic glucose, and the transition of glucokinase to the cytoplasm enables the phosphorylation of glucose. Glycogen genesis is activated as a result. The same metabolic pathway has been presumed with the mechanism for D-tagatose, an isomer of D-fructose.[28] Likewise, D-psicose could be expected to have an action to improve glucose tolerance; for example, it has been reported that fructokinase reacted with D-psicose and D-tagatose, and then their 1-phosphates interacted with the regulatory protein of liver glucokinase. The activation level of D-psicose 1-phosphate has also been shown to be second highest behind that of D-fructose 1-phosphate.[29–31] However, the function of glucokinase tends to be affected by insulin and glucagon, and the blood concentration of these ketoses would be different depending on the absorption rate in the digestive tract.[32] It will be complicated to clarify the actual effect of D-psicose on glucokinase and on glucose tolerance, hence making further studies necessary.

The safety of D-psicose was evaluated in subjects with normal blood glucose levels, who had continuously

ingested it for 12 weeks, by the parameters from blood examinations, urine analyses, physical examinations, and subjective symptoms.

Some parameters from the blood examinations and urine analyses showed significant variations within the standard ranges in a comparison between before and after treatment in each test and control group. There were significant differences in ALT between the groups after 8 weeks of treatment ($p < 0.05$) and in the urine specific gravity after 2 weeks ($p < 0.05$). However, their mean values were within the standard ranges and no serious variations were recognized in either case.

The effect of D-psicose on the indicators of hepatic functions during the treatment period was evaluated. CHE was significantly low within the standard range after 2 and 4 weeks, and LDH was also significantly low after 4 weeks in the test group. However, no variations were shown in AST, ALT, or γ-GTP, suggesting that the hepatic functions had not deteriorated. The effect on indicators of carbohydrate metabolism was also evaluated, and no variations were found in blood glucose, insulin, HbA1c and GA; therefore, 5 g of D-psicose ingestion by humans is considered not to affect the blood glucose level after meals nor the overall circadian variation. It has been reported that HbA1c was correlated with the average blood glucose level (the average of three values during fasting, three 2-h post-prandial values, and one before bedtime),[33] and the results of the meal-loading experiment showed no difference in the 2-h postprandial blood glucose levels between both the groups. These facts suggest one reason for there being no difference in HbA1c between both the groups in the long-term safety experiment.

D-Tagatose has been shown to transiently increase the plasma uric acid value by a single ingestion experiment in humans, although no accumulation was apparent from a repeated ingestion experiment.[34,35] Hence, we paid similar attention in this study of D-psicose, and no great variations were apparent in UA values in both groups during the treatment period and no abnormal findings that could indicate a clinical problem were recognized either in any subject.

There were significant variations found in the body fat percentage and diastolic blood pressure in the control group by the physical examination after 12 weeks of treatment, although no variation was apparent in the energy intake nor exercise level during the treatment period. This study was conducted from August to December, and it is known that the body fat and blood pressure of humans tend to rise in the transition from summer to winter. The increases in body fat and diastolic blood pressure observed in this study are therefore considered to have possibly been caused by seasonal factors such as air temperature variations. On the other hand, Matsuo *et al.* have reported the body fat reduction effect of D-psicose on rats,[36] and there was no significant increase of body fat observed in the test group in this study. The possibility that D-psicose could affect fat metabolism is therefore presumed. However, this point requires further discussion after considering such experimental conditions as the intake of water and measurement by an abdominal CT scan.

Sixteen subjects in the test group and 18 subjects in the control group reported abdominal symptoms and defecation conditions whose average incidence in both groups was 22.2%, with no significant differences between the groups. There was one subject in each group whose symptoms might have been associated with the treatment. It was revealed that one subject in the test group, who had worked irregularly for four days, had actually ingested several test meals at one sitting, resulting in the symptoms worsening. The subject discontinued the treatment for 12 d, but did not recover immediately, and no abdominal symptoms were observed by restarting the treatment after the subject had recovered. It was consequently difficult to judge a causal relationship between the symptoms and the test meal. Since the absorption rate of D-psicose is over 70% and the maximum no-effect level for diarrhea is assumed to be 0.5–0.6 g/kg of body weight, D-psicose is considered to be a monosaccharide that would hardly cause diarrhea by an overdose.[11,12] On the other hand, it is known that fructose causes defective absorption, and that its absorption rate is improved in a mixture with glucose.[19,20] This fact may provide a clue to the practical use of D-psicose to prevent such abdominal symptoms.

As other adverse events, there were two subjects in the control group who had abnormal values in the parameters from the clinical examination; however, both cases were judged to be not associated with the treatment. The frequency of occurrence of adverse events was the same in both groups.

D-Psicose is contained in common foods such as fruit juice (21.5 mg/100 g), meat sauce (15.8 mg/100 g), and Coke (38.3 mg/100 g). Around 206 mg in total is ingested per day in daily lives.[15] Considering the fact that D-tagatose is contained in such dairy products as high-temperature-pasteurized milk (300 mg/100 g), we presume that D-psicose would give the same meal experience as D-tagatose does.

Knowledge has been accumulated so far by various metabolism and safety experiments. No clinical problems were found in this long-term ingestion experiment, and it was confirmed that there were no particular problems in terms of the safety for healthy humans with a normal blood glucose level by the continuous ingestion of 5 g of D-psicose with a meal three times a day. However, there are some issues to consider, such as the effect of D-psicose ingestion in the long-term of years on glucose metabolism and the function of organs. Moreover, it was also confirmed that D-psicose had a suppressive effect on blood glucose elevation. We believe that a further study of D-psicose, which does not cause hypoglycemia, would be worthwhile to investigate it as a beneficial food for diabetes prevention and for people with borderline diabetes, including potential diabetes.

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