Postprandial Plasma Fructose Level Is Associated With Retinopathy in Patients With Type 2 Diabetes

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The aim of the present study was to investigate the association of fructose on microangiopathy in patients with diabetes. Postprandial plasma fructose concentrations and postprandial plasma glucose concentrations were simultaneously measured 3 times within a 24-hour period (2 hours after each meal) in 38 patients with type 2 diabetes that had been admitted to the hospital. The mean postprandial plasma fructose concentrations (MPPF) and the mean postprandial plasma glucose concentrations (MPPG) were calculated. Fructose was measured by gas chromatography–mass spectrometry (GCMS). Based solely on MPPF, we were able to divide the patients into three groups: the high MPPF (31.9 ± 6.5 μmol/L) group (n = 12), the middle MPPF (21.2 ± 1.8 μmol/L) group (n = 13), and the low MPPF (15.2 ± 2.4 μmol/L) group (n = 13). Prevalence and degree of retinopathy and nephropathy were then evaluated in the 3 different groups. A significant correlation was observed in the prevalence of proliferative diabetic retinopathy (PDR) among the 3 MPPF groups (*P* = .024). The prevalence of PDR was higher in the high MPPF group (75.0%) than in the middle and low MPPF groups (23.1% and 38.5%, respectively). Although not significantly different statistically, the prevalence of all degrees of retinopathy showed a tendency to be higher in the high MPPF group (83.3%) than in the middle and low MPPF groups (46.2% and 46.2%, respectively) (*P* = .081). Nephropathy prevalence also showed a tendency to be higher in the high MPPF group (66.7%) than in the middle and low MPPF groups (38.5% and 30.8%, respectively), although the differences were not significant. The prevalence of clinical albuminuria was not significantly different among the 3 groups, but there was a tendency for it to be higher in the low MPPF group (30.8%) than in the high and middle MPPF groups (16.7% and 0%, respectively). No significant differences in glycemic indicators and mean duration of diabetes were observed among the 3 groups. The increased prevalence of retinopathy in the high MPPF group suggests that fructose is associated with retinopathy in patients with type 2 diabetes.

FRUCTOSE is inferred to have an important role in the pathogenesis of diabetic microangiopathy, in view of nonenzymatic fructosylation of proteins,[1] the polyol pathway, and carbonyl stress. It has been reported that fructose concentrations are increased in many tissues of patients with diabetes[2] and in diabetic animals.[3-5] However, the pathological significance of fructose has not been confirmed because of the difficulty in measuring plasma fructose. We recently reported a newly developed method to detect small amounts of fructose in blood and urine samples.[6] We found that hyperglycemia was associated with increased fasting serum fructose concentrations in patients with diabetes.[6] Although we found that the plasma concentration of fructose was only about 1/500 of that of glucose as a free monosaccharide, we expected that fructose might be comparable to glucose in terms of mediating pathology through nonenzymatic reactions and downstream processes, because it has been reported that fructose is much more reactive in glycation than glucose.[1,7] We recently found that postprandial plasma fructose increased independently of postprandial plasma glucose, while fasting plasma fructose levels were a good correlate of fasting plasma glucose (FPG) levels.[6]

In the present study, we simultaneously measured postprandial plasma fructose concentrations and postprandial plasma glucose concentrations 3 times in a 24-hour period (2 hours after each meal) in patients with type 2 diabetes. Based solely on their mean postprandial plasma fructose concentration (MPPF), we were able to divide the patients into 3 groups. To determine whether or not fructose is associated with microangiopathy in diabetic patients, the prevalence and degree of retinopathy and nephropathy were then evaluated among the 3 groups.

MATERIALS AND METHODS

Thirty-eight inpatients with type 2 diabetes were recruited in Teikyo University Hospital (Tokyo, Japan). Informed consent, according to the principles in the Declaration of Helsinki, was obtained from each patient.

Postprandial plasma fructose concentrations and postprandial plasma glucose concentrations were simultaneously measured 3 times in a 24-hour period (2 hours after each meal) after patients were admitted to the hospital. The 3-time point examinations were started at least 24 hours after admission to the hospital. MPPF and mean postprandial plasma glucose concentrations (MPPG) from the 3 time points were calculated. Using the MPPF alone, we divided the patients into 3 groups: the high MPPF (31.9 ± 6.5 μmol/L) group (n = 12), the middle MPPF (21.2 ± 1.8 μmol/L) group (n = 13) and the low MPPF (15.2 ± 2.4 μmol/L) group (n = 13) (Fig 1). Prevalence and degree of retinopathy and nephropathy were then evaluated in the 3 groups.

Fasting plasma fructose concentration, FPG, hemoglobin A_{1c} (HbA_{1c}), serum 1,5-anhydroglucitol (1,5-AG), and daily urinary albumin excretion were measured once during each patient's admission. Systolic and diastolic blood pressure (BP) were also measured at the time of admission. Daily urinary albumin excretion was re-examined in the patients who had urinary tract infection, marked hypertension, or

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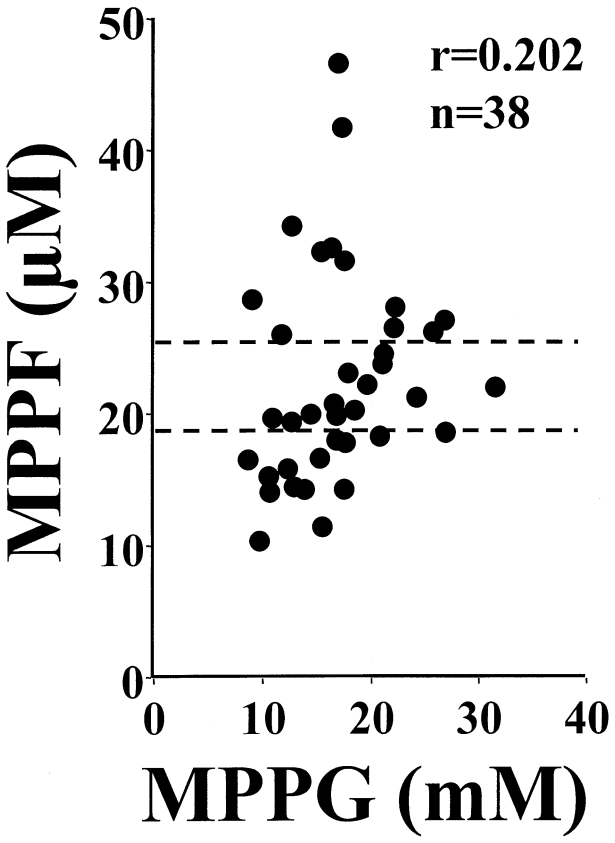

Fig 1. Correlation between MPPF and MPPG in patients with type 2 diabetes. No significant correlation was observed between MPPF and MPPG (r = 0.202, n = 38). Based solely on MPPF, we were able to divide the patients into 3 groups: a high MPPF (31.9 ± 6.5 μmol/L) group (n = 12), a middle MPPF (21.2 ± 1.8 μmol/L) group (n = 13), and a low MPPF (15.2 ± 2.4 μmol/L) group (n = 13). MPPF and MPPG were calculated from the fructose and glucose concentrations at 3 different time points (2 hours after each meal).

short-term hyperglycemia. Ophthalmologists examined all patients during the hospitalization to evaluate the degree of retinopathy.

Patients

All patients were admitted to our hospital from June 2001 to September 2001 and patients who were under 40 years old or above 80 years old were excluded from study participation.

All patients were hospitalized and underwent standard treatments designed to help the subjects achieve good glycemic control. Patients with severe renal dysfunction (serum creatinine $>$ 177 μmol/L) were excluded from study participation. It has been reported that patients with liver cirrhosis have much higher plasma fructose levels than normal subjects after oral fructose intake.[8] Therefore, patients with liver disease or liver dysfunction (serum aspartate aminotransferase $>$ 32 IU or alanine aminotransferase $>$ 35 IU) were also excluded. No patients received aldose reductase inhibitors before admission or during hospitalization.

Patients were placed on a therapeutic diet according to the guidelines of the Japan Diabetes Society during the hospitalization. Total amounts of daily dietary calories were calculated from (height [m])^2 × 550 kcal, in which 60% of the total calories consisted of carbohydrates, 20% proteins, and 20% fats. In regard to fructose, daily intake of fruits was fixed at 80 kcal and sucrose was less than 24 kcal. All diets were evaluated by certified clinical dieticians before delivery. The intake percentage of each diet in each patient was evaluated by a nurse in charge of the patient and patients who did not eat diets completely at the experimental day were also excluded. Honey, corn syrup, snacks, and so-called soft drinks were prohibited during hospitalization. We excluded patients when there were concerns as to whether or not they had strictly adhered to the dietary restrictions.

The high MPPF group was composed of 12 inpatients (7 women, 5 men) with a mean age of 65.8 years (range, 43 to 75 years) and a mean duration of diabetes of 13.7 years (range, 1 to 32 years). The mean HbA_{1c} level was 10.6% (range, 9.0% to 13.8%), and the mean body mass index (BMI) was 22.3 kg/m^2 (range, 17.9 to 25.7 kg/m^2). Three patients were treated by diet therapy alone, 2 patients received oral hypoglycemic agents, and 7 patients underwent insulin therapy.

The middle MPPF group was composed of 13 inpatients (6 women, 7 men) with a mean age of 61.2 years (range, 56 to 70 years) and a mean duration of diabetes of 8.4 years (range, 1 to 20 years). The mean HbA_{1c} level was 11.4% (range, 8.1% to 16.4%), and the mean BMI was 24.9 kg/m^2 (range, 17.6 to 32.5 kg/m^2). Six patients were treated by diet therapy alone, 2 patients received oral hypoglycemic agents, and 5 patients underwent insulin therapy.

The low MPPF group was composed of 13 inpatients (7 women, 6 men) with a mean age of 62.8 years (range, 50 to 74 years) and a mean duration of diabetes of 15.1 years (range, 1 to 30 years). The mean HbA_{1c} level was 10.2% (range, 7.3% to 16.0%), and the mean BMI was 25.1 kg/m^2 (range, 17.9 to 31.8 kg/m^2). Two patients were treated by diet therapy alone, 5 patients received oral hypoglycemic agents, and 6 patients underwent insulin therapy.

Sampling

Unless otherwise noted, blood samples were obtained from the patients after they had fasted for 12 hours. Plasma was separated by centrifugation immediately after collection and stored at −30°C until assayed. A 24-hour urine specimen was collected from each patient beginning at 7 AM. Sodium benzoate (5 g) was added as a preservative, and the specimen was refrigerated until assayed.

Determination of Plasma Fructose Concentration

Plasma fructose concentration was determined by gas chromatography–mass spectrometry (GCMS) according to the method we reported previously.[6] In brief, plasma samples (100 μL) were added to a fixed amount of $^{13}C_6$-fructose (Nippon Sanso, Tokyo, Japan) as the internal standard (20 μL). The mixture was applied onto a 2-layer column containing the acetate form (250 μL) of the anion exchanger (AG1-X8, Bio-Rad, Hercules, CA) on the bottom layer and the H form (250 μL) of the cation exchanger (AG50W-X8, Bio-Rad) on the top layer. Then, the column was washed with 1 mL distilled water, and the eluate was collected and evaporated. The dry residue was dissolved in 200 μL acetonitrile-water (80:20) and applied onto a high-performance liquid chromatography (HPLC) system fitted with a TSKgel Amide-80 column (Tosoh, Tokyo, Japan) heated at 80°C. The elution, acetonitrile-water (80:20) driven at 0.8 mL/min, was monitored by a refractive index detector, and the fraction corresponding to the peak for fructose 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 hour and was applied onto a reverse-phase HPLC column (Kromasil 100-5C18, Eka Chemicals AB, Bohus, Sweden) heated at 40°C. The elution, distilled water driven at 1.0 mL/min, was monitored by ultraviolet absorbance at 210 nm and 2 fractions corresponding to the 2 geometric isomers of fructose ethyloxime were collected and evaporated. The dry residue was peracetylated for GCMS analysis fitted with a fused silica capillary column (HP-5MS, Hewlett-Packard, Palo Alto, CA). The sample was loaded onto the column at

Table 1. Characteristics of Patients in the Three Groups

	High Group	Middle Group	Low Group
n	12	13	13
Sex (F/M)	7/5	6/7	7/6
Age (yr)	65.8 ± 19.1	61.2 ± 4.4	62.8 ± 7.8
BMI (kg/m^2)	22.3 ± 1.9	24.9 ± 4.5	25.1 ± 4.4
Systolic BP (mm Hg)	137.6 ± 17.8	141.8 ± 15.1	141.3 ± 17.6
Diastolic BP (mm Hg)	72.5 ± 7.5	75.0 ± 8.4	85.0 ± 9.0*
Mean duration of diabetes (yr)	13.7 ± 11.8	8.4 ± 7.6	15.1 ± 11.7
MPPF (μmol/L)	31.9 ± 6.5†	21.2 ± 1.8†	15.2 ± 2.4†
MPPG (mmol/L)	17.7 ± 5.5	19.3 ± 5.7	13.9 ± 3.6‡
Fasting plasma fructose (μmol/L)	13.3 ± 4.8	15.0 ± 4.3	9.0 ± 1.9†
FPG (mmol/L)	10.3 ± 3.9	11.8 ± 4.1	9.1 ± 2.8
HbA_{1c} (%)	10.6 ± 1.5	11.4 ± 2.3	10.2 ± 2.6
1,5-AG (μmol/L)	13.8 ± 11.1	12.1 ± 7.3	16.7 ± 9.4

NOTE. Data are n or mean ± SD. *$P < .01$ *v* high group and .05 *v* middle group. †$P < .01$ v other 2 groups. ‡$P < .01$ *v* middle group.

130°C, and the temperature was raised up to 250°C. The column was heated at the rate of 5°C/min from 180°C to 230°C and 20°C/min for other ramps. Elution of the derivative for fructose was observed at m/z = 271, while that for $^{13}C_6$-fructose was observed at m/z = 277. Thus, the amount of fructose in the original sample was calculated from the area ratio of the peaks of m/z = 271 to m/z = 277. The coefficients of variance were less than 3% (intra-assay) and less than 4% (interassay).

We measured fructose concentrations in a series of serum samples added to various amounts of glucose (final concentrations, 6 to 30 mmol/L) in order to examine the effect of varying concentrations of glucose on fructose recovery and we were able to confirm that glucose in the samples did not interfere with our fructose measurements (data not shown).

Determination of Serum 1,5-AG and HbA_{1c}

Serum 1,5-AG concentration (normal range, 78 to 256 μmol/L) was determined by an established enzymatic method using a 1,5-AG clinical test kit (Lana-1,5-AG, Nippon Kayaku, Tokyo, Japan). The HbA_{1c} level (normal range, 4.9%t o 5.9%) was assayed using HPLC (Auto A1c, Kyoto Daiichi Kagaku, Kyoto, Japan).

Prevalence and Degree of Retinopathy and Nephropathy

All patients were examined at least one time during the hospitalization by ophthalmologists with experience in the management of diabetic retinopathy. The degree of retinopathy was evaluated by using dilated indirect ophthalmoscopy coupled with biomicroscopy. Diabetic retinopathy was classified into 3 degrees, ie, no abnormalities, nonproliferative diabetic retinopathy, and proliferative diabetic retinopathy (PDR).

Daily urinary albumin excretion was examined once in each patient during the admission. However, the patients who had urinary tract infection, marked hypertension, or short-term hyperglycemia were reexamined when their conditions improved. Albumin excretion was classified into 3 categories, ie, normal (<30 mg/d), microalbuminuria (30 to 299 mg/d), and clinical albuminuria (>300 mg/d).

Statistical Analysis

Data are presented as the mean ± SD. For normally distributed data, Bonferroni/Dunn's procedure as a multiple comparison procedure test was performed. For any difference in distribution among the 3 groups, Fisher's protected least significant difference tests were performed. Correlations between groups were estimated by Pearson's correlation coefficient. Univariate analysis was performed using the chi-square test for independence or the Fisher's exact probability test. *P* values less than .05 were considered statistically significant.

RESULTS

Correlation Between MPPF and MPPG

No significant correlation was observed between the MPPF and the MPPG ($r = 0.202$, n = 38) (Fig 1). This lack of a correlation is quite different from the significant correlation between the fasting serum fructose and FPG that we previously reported.[6] However, based entirely on the MPPF, we were able to divide the patients into 3 groups—the high MPPF (31.9 ± 6.5 μmol/L) group (n = 12), the middle MPPF (21.2 ± 1.8 μmol/L) group (n = 13), and the low MPPF (15.2 ± 2.4 μmol/L) group (n = 13).

Characteristics of Patients in the High, Middle, and Low MPPF Groups

Although significant differences in MPPF were observed among the 3 groups ($P < .01$ *v* the other 2 groups), MPPG was not significantly different between the high and low MPPF groups (Table 1). MPPG was significantly higher for the middle MPPF group as compared to that seen for the low MPPF group ($P < .01$). No significant difference was observed in FPG, HbA_{1c}, and 1,5-AG among the 3 groups. Although the mean duration of diabetes was not significantly different among the 3 groups, it showed a tendency to be higher in the low MPPF group than in the middle MPPF group. The mean diastolic BP was significantly higher in the low MPPF group than in the high ($P < .01$) and middle ($P < .05$) MPPF groups. Fasting plasma fructose was significantly lower in the low MPPF group as compared to that seen in the middle ($P < .01$) and high ($P < .01$) MPPF groups.

Prevalence of Retinopathy and Nephropathy in the High, Middle, and Low MPPF Groups

To determine the influence of fructose on microangiopathy in patients with diabetes, prevalence and degree of diabetic retinopathy and nephropathy were evaluated among the 3 groups (Table 2). A significant correlation was observed in the prevalence of PDR among the 3 MPPF groups ($P = .024$), ie,

Table 2. Prevalences of Retinopathy and Nephropathy in the Three Groups

	High Group (n = 12)	Middle Group (n = 13)	Low Group (n = 13)	*P* Value
Retinopathy	10 (83.3%)	6 (46.2%)	6 (46.2%)	.081
PDR	9 (75.0%)	3 (23.1%)	5 (38.5%)	.024
Nephropathy	8 (66.7%)	5 (38.5%)	4 (30.8%)	.168
Clinical albuminuria	2 (16.7%)	0 (0%)	4 (30.8%)	.098

NOTE. Data are n. Univariate analyses were done with the chi-square test for independence.

the prevalence of PDR was higher in the high MPPF group than the middle and low MPPF groups. Although not statistically significantly, the prevalence of all degrees of retinopathy showed a tendency to be higher in the high MPPF group than in the middle and low MPPF groups ($P = .081$). When we consider the middle and low MPPF groups as a group, the prevalence of PDR ($P = .016$) and all degrees of retinopathy ($P = .040$) were significantly higher in the high MPPF group than in the other MPPF group for which there was no significant difference in the mean age, duration of diabetes, MPPG, and glycemic indicators as compared to the high MPPF group (data not shown). There was also a tendency for the prevalence of nephropathy to be higher in the high MPPF group than in the middle and low MPPF groups although this was not statistically significant. Additionally, while the prevalence of clinical albuminuria was not significantly different among the 3 groups, it showed a tendency to be higher in the low MPPF group than in the high and middle MPPF groups.

Correlations Between MPPF and Other Indicators

To determine the factors accompanied by the change of MPPF, correlations between MPPF and other indicators were examined (Table 3). A significant correlation was observed between MPPF and fasting plasma fructose ($r = 0.429$) or BMI ($r = -0.337$). No other indicators were significantly correlated with MPPF.

DISCUSSION

Two large epidemiological studies describing the onset and progression of diabetic complications over long periods of time have been reported in the last decade, and a relationship between development of diabetic complications and glycemic exposure has been established.[9,10] However, the influence of fructose on microangiopathy in patients with diabetes has not been previously reported.

Table 3. Correlations Between MPPF and Other Indicators

	Correlation Coefficient (*r*) (n = 38)	*P* Value
Age (yr)	0.188	NS
BMI (kg/m^2)	−0.337	<.05
Systolic BP (mm Hg)	−0.093	NS
Diastolic BP (mm Hg)	−0.277	NS
Mean duration of diabetes (yr)	0.057	NS
FPG (mmol/L)	0.112	NS
HbA_{1c} (%)	0.072	NS
1,5-AG (μmol/L)	−0.183	NS
MPPG (mmol/L)	0.202	NS
Fasting plasma fructose (μmol/L)	0.429	<.01

NOTE. Data are n.

Several risk factors have been reported for the progression of diabetic microangiopathy, especially for retinopathy, in patients with type 1 diabetes. The Wisconsin Epidemiologic Study of Diabetic Retinopathy reported that an increased risk of PDR was associated with more severe baseline retinopathy, higher HbA_{1c} at baseline, and an increase in the HbA_{1c} between the baseline and the 4-year follow-up examination.[11] The European Community Concerted Action on the Epidemiology and Prevention of Diabetes (EURODIAB) Prospective Complications Study reported that HbA_{1c}, diabetes duration, age at diagnosis less than 12 years, diastolic BP above 84 mm Hg, and waist-to-hip ratio were all independent predictors for progression to PDR.[12] Lövestam-Adrain et al[13] reported that patients who developed any retinopathy had higher mean HbA_{1c} and diastolic BP levels over time compared to those who remained stable.

In regard to type 2 diabetes, the United Kingdom Prospective Diabetes Study recently reported that not only lowering blood glucose levels but also lowering BP levels significantly reduced the risk of diabetic microangiopathy in type 2 diabetes.[10] Voutilainen-Kaunisto et al[14] reported that visual acuity was inversely correlated to the HbA_{1c} value of the 5-year examination in 133 type 2 diabetic patients.

With regard to risk factors for the progression of diabetic microangiopathy mentioned above, we found no significant differences in the glycemic levels and duration of diabetes among the 3 groups in the present study. The mean diastolic BP at admission was significantly higher in the low MPPF group than in the middle and high MPPF groups. However, the prevalence of PDR and all degrees of retinopathy showed a tendency to be lower in the low MPPF group than in the high MPPF group. Both the prevalence of PDR and duration of diabetes in the low MPPF group showed tendencies to be higher than that seen in the middle MPPF group. The longer duration of diabetes in the low MPPF group might be responsible for the greater increase in the prevalence of PDR in the low MPPF group versus that seen in the middle MPPF group. Indeed, the prevalence of clinical albuminuria showed a tendency to be higher in the low MPPF group than in the middle MPPF group.

In the present study, no significant correlation was observed between the MPPF and the MPPG values. This lack of a correlation is quite different from the significant correlation between the fasting serum fructose and FPG that we previously

reported.[6] Fructose has unique metabolic properties when compared with glucose, both in its rapid uptake by the liver, and its entry into the glycolysis or gluconeogenesis pathways at the triose phosphate level after bypassing the phosphofructokinase regulatory step where glucose usually enters.r Indeed, fructose disappears from the circulation twice as fast as glucose, with its half-life being about 18 minutes as compared with 43 minutes for glucose.[16] We believe that there is no significant correlation between the MPPF and the MPPG that depends on the different metabolic properties of the 2 monosaccharides.

When discussing postprandial plasma fructose concentrations in patients with diabetes, we need to consider not only exogenous fructose, ie, oral intake, but also endogenous fructose. We previously reported that plasma fructose in patients with type 2 diabetes significantly increased after an oral glucose loading that contained no fructose.[17] This result suggests that fructose is generated endogenously in patients with type 2 diabetes. We speculate that the variation of MPPF observed in the present study may be caused by variations in the endogenous production of fructose. These variations could include differences in the activity of the polyol pathway, where fructose is the end product and is activated by hyperglycemia, or potential shunting from phosphorylated fructose glycolytic intermediates.

On the other hand, as it is well known that postprandial plasma glucose or post-loading plasma glucose of the glucose tolerance test demonstrates varying concentrations in humans,[18,19] postprandial plasma fructose could also be expected to demonstrate varying concentrations in subjects. In the present study, all inpatients did not take equivalent meals or formulae such as that used for oral glucose tolerance tests. All inpatients were given a therapeutic diet according to the guidelines of the Japan Diabetes Society that was based on traditional Japanese foods, and which included small amounts of fruits and sucrose. We confirmed that all inpatients were offered similar amounts of fructose and ate them completely throughout the day during our experimental periods. Therefore, we believe that the MPPF data in the present study is meaningful.

Although the prevalence of PDR was higher in the high MPPF group than in the low MPPF group, the prevalence of clinical albuminuria showed a tendency to be lower in the high MPPF group than in the low MPPF group. These results may indicate that postprandial plasma fructose more significantly influences the progression of retinopathy than the progression of nephropathy. Agardh et al[20] reported that 35% of patients with PDR did not show any detectable signs of nephropathy and they concluded that the factors underlying the development of retinopathy and nephropathy might be of different origins.

To determine the factors accompanied by the change of MPPF, we examined correlations between MPPF and other indicators. BMI showed a strong negative correlation with the level of MPPF. This finding is consistent with the result that the mean BMI showed a tendency to be lower in the high MPPF group than in the middle and low MPPF groups. Fasting plasma fructose showed a significant correlation with the level of MPPF. This finding is consistent with the result that fasting plasma fructose was significantly lower in the low MPPF group than in the high and middle MPPF groups. It also provided us with information on how to divide fasting plasma fructose values into groups in order to reveal the relationship between fasting plasma fructose and diabetic microangiopathy. We expect that the examination of much larger number of the subjects in future studies may demonstrate significant correlations between fasting plasma fructose levels and diabetic microangiopathy. We also need to consider that the present study was a retrospective one, and therefore we need to design a prospective study to confirm whether or not postprandial plasma fructose levels influence microangiopathy in diabetic patients.

In conclusion, the high MPPF group had an increased prevalence of retinopathy. This result suggests that the postprandial plasma fructose level is associated with retinopathy in patients with type 2 diabetes.

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