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Post-prandial hyperglycemia is an important predictor of the incidence of diabetic microangiopathy in Japanese type 2 diabetic patients ☆

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Abstract

Diabetic microangiopathy is often observed in diabetic patients, but there is little evidence regarding the relationship between post-prandial glycemia or insulinemia and the incidence of diabetic microangiopathy. In this study, to elucidate the relationship between post-prandial glycemia (or insulinemia) and diabetic microangiopathy, we performed a cross-sectional study of 232 subjects with type 2 diabetes mellitus who were not being treated with insulin injections. A multiple regression analysis showed that post-prandial hyperglycemia independently correlated with the incidence of diabetic retinopathy and neuropathy. Post-prandial hyperglycemia also correlated, although not independently, with the incidence of diabetic nephropathy. In addition, interestingly, post-prandial hypoinsulinemia independently correlated with the incidence of diabetic retinopathy, although not correlated with diabetic neuropathy or nephropathy. In conclusion, post-prandial hyperglycemia, rather than fasting glycemia or hemoglobin A1c levels, is an important predictor of the incidence of diabetic microangiopathy in Japanese type 2 diabetic patients.

Keywords: Diabetes; Post-prandial hyperglycemia; Post-prandial hypoinsulinemia; Diabetic microangiopathy; Retinopathy; Nephropathy; Neuropathy

It is well known that post-challenge hyperglycemia, which refers to high blood glucose levels following a 75 g oral glucose load, is related to the progression of diabetic macroangiopathy [1] and to mortality rate in subjects with impaired glucose tolerance and type 2 diabetes mellitus [2–4]. In addition to post-challenge hyperglycemia, the importance of post-prandial hyperglycemia as a risk factor of diabetic macroangiopathy is suggested from the results of various epidemiological studies [5–7]. However, there have only been a few reports regarding the association between post-prandial hyperglycemia and diabetic microangiopathy in human subjects. In this study, we examined whether there is a relationship between post-prandial glucose (or insulin) levels and the incidence of diabetic microangiopathy in Japanese type 2 diabetic patients, and found that post-prandial hyperglycemia, rather than fasting glycemia or hemoglobin A1c levels, is an important predictor of the incidence

☆ *Abbreviations:* PPG, post-prandial plasma glucose; PPI, post-prandial plasma insulin; PCG, post-challenge plasma glucose; PCI, post-challenge plasma insulin; WHO, World Health Organization; FPG, fasting plasma glucose; FPI, fasting plasma insulin; ECG, electric cardiograms; CVRR, coefficient variation of ECG R-R interval; AER, albumin excretion rate; DCCT, diabetes control and complications trial; 1,5-AG, 1,5-anhydro-D-glucitol; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor; ET-1, endothelin-1; NDR, non-diabetic retinopathy; SDR, simple diabetic retinopathy; PDR, proliferative diabetic retinopathy.

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of diabetic microangiopathy such as retinopathy, neuropathy, and nephropathy.

Methods

Study cohort. We recruited 232 Japanese patients with type 2 (non-insulin-dependent) diabetes mellitus aged between 24 and 82 years, who were admitted to Osaka Prefectural General Hospital for the education of diabetes. The assessment of type 2 diabetes was based on World Health Organization (WHO) criteria. Patients were recruited for the study when they met the following criteria: (1) no episode of ketoacidosis, (2) no treatment with insulin injections, (3) absence of overt diabetic nephropathy (daily urinary protein excretion levels: less than 1 g/24 h) or other renal diseases such as glomerulonephritis, nephrotic syndrome, and renal failure, and (4) absence of acute coronary heart disease, cerebral vascular disease, or peripheral artery disease after careful evaluation of clinical records.

During the first week after admission, we did not change the patients' prescription for the treatment of diabetes, hyperlipidemia, and hypertension, and treated them in the same way as they had been just before admission. One hundred and thirty patients were treated with diet alone and 102 patients were treated with oral hypoglycemic agents (95 received a sulfonylurea, 38 received an α-glucosidase inhibitor, 16 received biguanide, and 7 received thiazolidinedione). Antihypertensive drugs were given to 75 patients (11 received diuretics, 12 received β-blockers, 2 received α-blockers, 47 received calcium channel blockers, 23 received angiotensin-converting enzyme inhibitors, and 4 received angiotensin-2 receptor blockers). Antihyperlipidemic drugs were administered to 41 patients (5 received clofibrates, 2 received probucol, and 34 received 3-hydroxyl-3-methylglutaryl-CoA reductase inhibitors).

Two to four days before admission, patients were given an oral load of 75 g glucose. Blood was withdrawn using standard laboratory techniques before, and 60 and 120 min after the glucose load for the determination of plasma glucose and insulin concentrations. Within 2–4 days after admission, blood samples were taken for analyses of fasting plasma glucose (FPG), fasting plasma insulin (FPI), hemoglobin A_{1C} (HbA_{1C}), serum total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and serum triglyceride levels. Two hours after the intake of an isocaloric mixed breakfast (10 kcal/kg of body weight, 57% carbohydrate, 15% fat, and 28% protein), representative of a standard Japanese breakfast, blood was withdrawn to measure post-prandial plasma glucose (PPG) and post-prandial plasma insulin (PPI) levels. To reflect daily glycemic excursion, strenuous exercise was prohibited by providing a written direction to each patient before post-prandial blood withdrawal; the patients were permitted only mild exercise, which is a level equal to daily exercise of each subject. Systolic and diastolic blood pressure was measured using a mercury sphygmomanometer. Exposure to smoking was estimated as the mean number of cigarettes smoked daily. Laboratory methods were kept constant throughout the study period.

Within a week after admission, retinopathy was assessed through dilated pupils by ophthalmologists, and classified as no evidence of diabetic retinopathy (NDR), simple diabetic retinopathy (SDR), pre-proliferative retinopathy (pre-PDR), or proliferative retinopathy (PDR). If the eyes were asymmetric, we used data from the eye that was graded as having the worse retinopathy. Electro cardiograms (ECGs) were taken to calculate the coefficient variation of ECG R-R interval (CVRR), as an index of cardiac autonomic nervous function. Albumin excretion rate (AER) was measured using a fresh 24-h urine collection sample, as an index of diabetic nephropathy. Upon completion of each collection, a midstream specimen of urine was examined by microscopy or by culturing to exclude urinary tract infection and hematuria. Albumin concentrations were determined by radioimmunoassay (RIA).

Statistical analyses. Data are presented as means ± SD. The laboratory data were compared by the unpaired *t* test or Mann–Whitney's *U* test. Stepwise multivariate regression analyses, including sex and smoking, were performed to evaluate the relationship between possible risk factors and diabetic nephropathy and cardiac autonomic nerve dysfunction in diabetic patients. Multiple logistic model analysis was performed to evaluate the relationship between possible risk factors and diabetic retinopathy where NDR was set at 0, and SDR, pre-PDR, and PDR were set at 1. All analyses were conducted using the SPSS statistical package (SPSS, IL, USA).

Results

Post-prandial plasma glucose levels are significantly higher in type 2 diabetic patients with diabetic microangiopathy

The patients' baseline characteristics are shown in Table 1. The mean age of the 232 enrolled subjects with type 2 diabetes was 57.3 ± 11.5 years. The duration of diabetes was 7.2 ± 7.5 years. To examine the association of plasma glucose and insulin levels with the incidence of diabetic microangiopathy, we compared post-prandial and post-challenge plasma glucose and insulin concentrations between patients with and without diabetic retinopathy, neuropathy, and nephropathy. As shown in Table 2 and Fig. 1, post-prandial and post-challenge plasma glucose concentrations were significantly higher in subjects with diabetic retinopathy than in subjects without retinopathy. On the other hand, post-prandial and post-challenge plasma insulin concentrations were significantly lower in subjects with diabetic retinopathy than in subjects without retinopathy. Post-prandial and post-challenge plasma glucose concentrations were significantly higher in subjects with a

Table 1
Baseline characteristics of the patients[a]

Characteristic	Sulfonylurea treatment	Diet alone
Total number of patients	130	102
Sex (F/M)	67/63	53/49
Age (years)	58.8 ± 10.1	55.4 ± 12.9*
Duration of diabetes (years)	8.9 ± 8.2	5.1 ± 5.9*
Body-mass index (kg/m^2)[b]	24.2 ± 4.31	25.9 ± 4.39*
Glycosylated hemoglobin (%)	8.40 ± 1.33	7.89 ± 1.45*
Blood pressure		
Systolic (mmHg)	122.9 ± 17.6	121.9 ± 15.2
Diastolic (mmHg)	77.2 ± 11.4	76.7 ± 10.2
Cholesterol		
Total (mmol/L)	5.1 ± 0.9	5.3 ± 1.1
Low-density lipoprotein (mmol/L)	3.2 ± 0.9	3.2 ± 1.0
High-density lipoprotein (mmol/L)	1.3 ± 0.6	1.3 ± 0.9
Triglyceride (mmol/L)	1.5 ± 0.8	1.6 ± 1.0
Coefficient variation of ECG R-R interval (%)	2.45 ± 1.12	2.49 ± 1.07
Retinopathy		
NDR (no. of subjects)	93	87
SDR (no. of subjects)	27	10*
Pre-PDR, PDR (no. of subjects)	10	5*
Urine albumin excretion rate (mg/g creatinine)	39.5 ± 64.2	27.2 ± 49.7

Abbreviations: NDR, non-diabetic retinopathy; SDR, simple diabetic retinopathy; PDR, proliferative diabetic retinopathy.

[a] Values expressed with plus/minus signs are means ± SD.

[b] The body-mass index is the weight in kilograms divided by the square of the height in meters.

* $p < 0.05$ for the comparison of sulfonylurea treatment with diet therapy alone.

Table 2
Comparison of post-prandial and post-challenge plasma glucose and insulin concentrations between patients with and without diabetic microangiopathy

	Retinopathy		Neuropathy		Nephropathy	
	NDR	SDR, pre-PDR, PDR	CVRR ≧ 2.00 (%)	CVRR < 2.00 (%)	AER < 20 (μg/min)	AER ≧ 20 (μg/min)
PCG (mmol/L)	18.6 ± 5.6	20.6 ± 5.3*	18.5 ± 5.3	20.3 ± 6.2†	18.6 ± 5.7	20.1 ± 5.4‡
PPG (mmol/L)	12.4 ± 3.9	15.4 ± 4.3***	12.4 ± 3.9	14.4 ± 4.3 ††	12.5 ± 4.1	14.1 ± 4.1‡‡
PCI (pmol/L)	220.4 ± 164.9	133.2 ± 82.3**	207.9 ± 155.2	193.2 ± 159.5	206.7 ± 150.6	195.4 ± 169.8
PPI (pmol/L)	213.5 ± 120.2	124.6 ± 61.9***	209.1 ± 128.0	176.9 ± 90.8	207.6 ± 123.6	173.4 ± 97.7

Values are means ± SD.
Abbreviations: PPG, postprandial plasma glucose; PPI, postprandial plasma insulin; NDR, non-diabetic retinopathy; SDR, simple diabetic retinopathy; PDR, proliferative diabetic retinopathy; CVRR, coefficient variation of ECG R-R interval.
* $p = 0.02$ vs NDR.
** $p = 0.002$ vs NDR.
*** $p < 0.0005$ vs NDR.
† $p = 0.01$ vs CVRR ≧ 2.00 (%).
†† $p < 0.0005$ vs CVRR ≧ 2.00 (%).
‡ $p = 0.05$ vs AER < 20 (μg/min).
‡‡ $p = 0.005$ vs AER < 20 (μg/min).

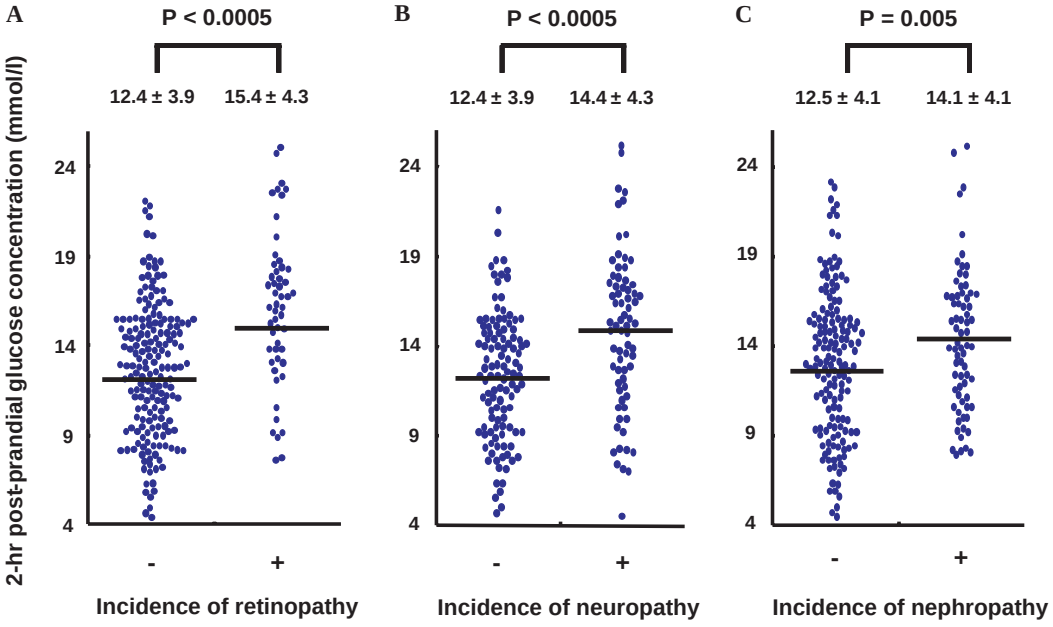

Fig. 1. Comparison of 2-h post-prandial plasma glucose concentrations between subjects with and without the incidence of diabetic retinopathy (A), neuropathy (B), and nephropathy (C).

CVRR of less than 2.00%, or with an AER of more than 20 μg/min, although there was no difference in post-prandial and post-challenge plasma insulin concentrations between patients with and without diabetic neuropathy or nephropathy. Taken together, post-prandial as well as post-challenge plasma glucose levels were significantly higher in Japanese type 2 diabetic patients with diabetic microangiopathy such as retinopathy, neuropathy, and nephropathy.

Post-prandial hyperglycemia and hypoinsulinemia are important predictors of the incidence of diabetic retinopathy

Since HbA1c, post-prandial glucose and insulin levels, post-challenge glucose and insulin levels, fasting plasma glucose and insulin levels, and duration of diabetes are closely linked, we performed multiple logistic model analyses including sex, smoking, blood pressure, and serum lipid profile, to identify the independent and important predictors of the incidence of diabetic retinopathy and possible risk factors (Table 3). Also, it is noted that, in multiple regression analyses, the significance of several factors can be lost when there is a very close correlation among these several factors and also another factor has a stronger correlation. Systolic blood pressure (odds ratio 1.05, 95% confidence interval 1.026–1.075, $p < 0.0001$), post-prandial plasma glucose concentration (odds ratio 1.01, 95% confidence interval 1.005–1.016, $p = 0.0002$), post-prandial plasma insulin concentration (odds ratio 0.964, 95% confidence interval 0.939–0.989, $p = 0.0049$), and duration of diabetes (odds ratio 1.067, 95% confidence interval 1.018–1.117, $p = 0.0063$) independently correlated with the incidence of diabetic retinopathy. In this analysis, significance in cor-

Table 3
Data from multivariate analyses evaluating association between the microangiopathy and various clinical parameters

Parameter	Retinopathy[a]				CVRR[b]				Log AER[b]			
	75 g OGTT		Standard meal		75 g OGTT		Standard meal		75 g OGTT		Standard meal	
	Odds ratio (95% CI)	*p* value	Odds ratio (95%CI)	*p* value	Partial correlation coefficient	*p* value	Partial correlation coefficient	*p* value	Partial correlation coefficient	*p* value	Partial correlation coefficient	*p* value
Age (years)	NS	NS	NS	NS	−0.2978	0.0007	−0.3446	<0.0001	NS	NS	NS	NS
Duration (years)	1.114 (1.053–1.178)	0.0002	1.067 (1.018–1.117)	0.0063	NS	NS	NS	NS	NS	NS	NS	NS
BMI (kg/m^2)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
FPG (mmol/L)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0.2010	0.0023
FPI (pmpl/L)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
PCG (mmol/L)	NS	NS	ND	ND	NS	NS	ND	ND	NS	NS	ND	ND
PPG (mmol/L)	ND	ND	1.010 (1.005–1.016)	0.0002	ND	ND	−0.1887	0.0080	ND	ND	NS	NS
PCI (pmol/L)	0.963 (0.938–0.988)	0.0044	ND	ND	NS	NS	ND	ND	NS	NS	ND	ND
PPI (pmol/L)	ND	ND	0.964 (0.939–0.989)	0.0049	ND	ND	NS	NS	ND	ND	NS	NS
HbA1C (%)	NS	NS	NS	NS	NS	NS	NS	NS	0.1784	0.0098	NS	NS
sBP (mmHg)	1.068 (1.037–1.101)	<0.0001	1.050 (1.026–1.075)	<0.0001	NS	NS	NS	NS	0.1535	0.0261	0.2334	0.0004
dBP (mmHg)	0.951 (0.911–0.994)	0.0248	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
T-CHO (mmol/L)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
TG (mmol/L)	NS	NS	NS	NS	−0.1855	0.0094	NS	NS	0.1387	0.0445	NS	NS
R^2					0.1504		0.1957		0.2831		0.1173	

Abbreviation: CVRR, coefficient variation of ECG R-R interval; OGTT, oral glucose tolerance test; BMI, body-mass index; FPG, fasting plasma glucose; FPI, fasting plasma insulin; PCG, postchallenge glucose; PPG, postprandial plasma glucose; PCI, postchallenge insulin; PPI, postprandial plasma insulin; sBP, systolic blood pressure; dBP, diastolic blood pressure; T-CHO, total-cholesterol; TG, triglyceride; ND, not determined; NS, not significant.

[a] Evaluated by multiple logistic regression model analysis was performed.

[b] Evaluated by stepwise multivariate regression analysis was performed.

relation between HbA1c levels and the incidence of retinopathy was lost because post-prandial glucose levels had a stronger correlation with the incidence of diabetic neuropathy rather than HbA1c levels. Furthermore, multiple logistic model analyses including post-challenge glucose and insulin concentrations showed that systolic blood pressure (odds ratio = 1.068, $p < 0.0001$), duration of diabetes (odds ratio = 1.114, $p = 0.0002$), 2-h post-challenge plasma insulin concentration (odds ratio = 0.963, $p = 0.0044$), and diastolic blood pressure (odds ratio = 0.951, $p = 0.0248$) independently correlated with the incidence of diabetic retinopathy. In addition to this, post-prandial insulin levels also independently correlated with the incidence of diabetic retinopathy. Fig. 2 shows the association between 2-h post-prandial insulin concentration, 2-h post-prandial glucose concentration, and the incidence of diabetic retinopathy. The highest incidence of diabetic retinopathy was found at both the high tertile of 2-h post-prandial glucose concentration and the low tertile of 2-h post-prandial insulin concentration. On the other hand, the lowest incidence of diabetic retinopathy was found at both the low tertile of 2-h post-prandial glucose concentration and the high tertile of 2-h post-prandial insulin concentration. Taken together, post-prandial hyperglycemia and hypoinsulinemia are independent and important predictors of the incidence of diabetic retinopathy.

Post-prandial hyperglycemia is an important predictor of the incidence of diabetic neuropathy and nephropathy

In addition, to evaluate the correlation between cardiac autonomic neuropathy and risk factors, we performed stepwise multivariate regression analysis of the coefficient variation of ECG R-R intervals (CVRR), an index of cardiac autonomic neuropathy. As shown in Table 3, this analysis showed that age ($p < 0.0001$), 2-h post-prandial plasma glucose levels ($p = 0.0080$), independently correlate with cardiac autonomic neuropathy. In this analysis, significance of HbA1c levels was lost because post-prandial glucose levels had a stronger correlation with the incidence of diabetic neuropathy rather than HbA1c. On the other hand, multiple regression analysis of post-challenge plasma glucose and insulin concentrations showed that age ($p = 0.0007$), and triglyceride levels ($p = 0.0094$), but not post-challenge plasma glucose and insulin concentrations, independently correlated with cardiac autonomic neuropathy. Taken together, post-prandial hyperglycemia is an independent and important predictor of the incidence of diabetic neuropathy.

Similarly, to evaluate the correlation of diabetic nephropathy and risk factors, we performed stepwise multivariate regression analysis including the urinary excretion rate of albumin, an index of diabetic nephropathy. As

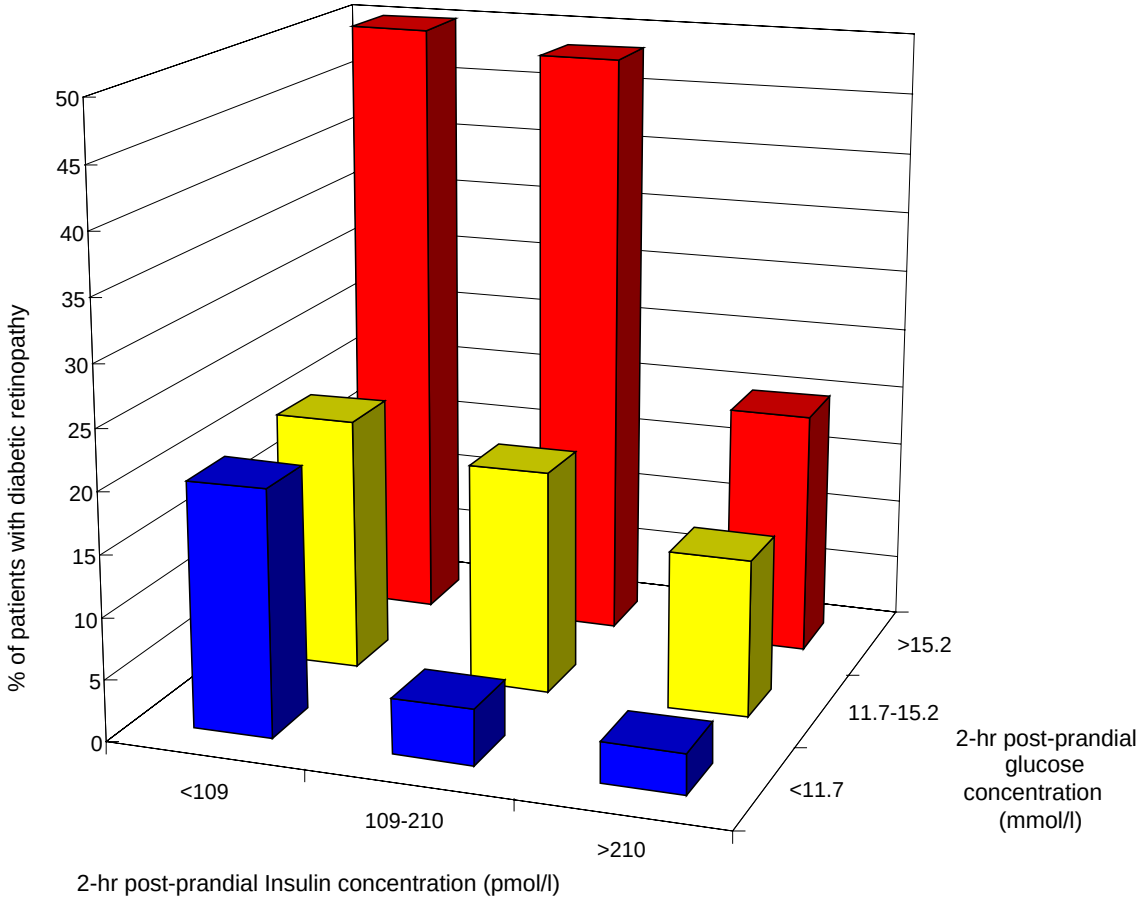

Fig. 2. Incidence of diabetic retinopathy analyzed by tertiles of 2-h post-prandial insulin concentrations and 2-h post-prandial glucose concentrations.

shown in Table 3, this analysis showed that systolic blood pressure ($p = 0.0004$), fasting plasma glucose ($p = 0.0023$) independently correlate with diabetic nephropathy. This analysis also suggests that post-prandial hyperglycemia is not an independent predictor of the incidence of diabetic nephropathy. As shown in Table 2, however, post-prandial hyperglycemia could be an important predictor of the incidence of diabetic nephropathy. Thus, we assume we should conclude that post-prandial hyperglycemia is an important, although not independent, predictor of the incidence of diabetic nephropathy.

Discussion

The importance of post-prandial hyperglycemia as a risk factor of diabetic macroangiopathy has been suggested from the results of various epidemiological studies [5–7]. However, there have only been a few reports on the relationship between diabetic microangiopathy and post-prandial hyperglycemia in human subjects. An analysis of the diabetes control and complications trial (DCCT) showed that none of the 3 different post-prandial blood glucose levels may predict the incidence of diabetic retinopathy in type 1 diabetic patients [8]. In this study, we first demonstrated that post-prandial hyperglycemia, rather than fasting plasma glucose levels and HbA_{1C} levels, is a better indicator of daily glycemic excursion, which is responsible for the diabetic retinopathy and cardiac autonomic neuropathy in type 2 diabetic patients.

Epidemiological and intervention studies have clearly indicated the importance of HbA_{1C} levels in predicting long-term diabetic complications. In a further analysis of the DCCT results [9–11], at similar mean HbA_{1C} values, the worsening of diabetic retinopathy in type 1 diabetic patients on conventional treatment was greater than in patients on intensified insulin treatment. In addition, we previously described that subjects with type 2 diabetes treated by conventional insulin treatment possessed a significantly lower value of 1,5-anhydro-D-glucitol (1,5-AG) which indicates higher glycemic excursion than those treated by multiple insulin injections [12,13]. Because these data imply that diabetic subjects treated by conventional insulin therapy show profound post-prandial hyperglycemia compared with those treated by multiple insulin injections, we assume that diabetic retinopathy results from the extent of post-prandial glucose excursions. In addition, it has been reported that hyperglycemia increases the blood concentration of some growth factors such as platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), which lead to vascular construction and neovascularization [14]. In addition, it is known that hyperglycemia increases apoptosis in retinal pericytes and endothelial cells [15,16]. Thus, although not examined in this study, it is plausible that post-prandial hyperglycemia contributes to the progression of diabetic retinopathy at least in part through the increased expression of several growth factors and an induction of apoptosis in retinal cells.

The multiple regression analyses pointed out that post-prandial hypoinsulinemia independently correlates with diabetic retinopathy and cardiac autonomic neuropathy (Table 3). This observation has not been reported previously, probably because of the insufficient number of post-prandial insulin determinations. It has been reported that physiological concentrations of insulin rescue cultured optic nerve oligodendrocytes from apoptosis and are necessary for the survival of retinal ganglion cells in culture [17]. Thus, although not examined in this study, we assume that post-prandial hypoinsulinemia contributes to the incidence of diabetic retinopathy at least in part through the increased expression of several growth factors and an induction of apoptosis in retinal cells.

In conclusion, post-prandial hyperglycemia, rather than fasting glycemia or HbA1c levels, is a stronger predictor of the incidence of each diabetic microangiopathy in Japanese type 2 diabetic patients.

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