Correlations of Fasting and Postprandial Blood Glucose Increments to the Overall Diurnal Hyperglycemic Status in Type 2 Diabetic Patients: Variations with Levels of HbA1c

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Abstract. Studies from overseas have indicated that postprandial glucose excursions are predominant in subjects with moderate hyperglycemia, while fasting hyperglycemia become the predominant abnormality with worsening of hyperglycemia; however, few studies have yet investigated the correlation between HbA1c and fasting and/or postprandial hyperglycemia in Japanese subjects. We investigated the correlation between fasting and postprandial hyperglycemia and the overall diabetic status, as assessed by measurement of HbA1c, in Japanese patients with type 2 diabetes. Blood glucose (BG) concentrations were determined in the fasting state (7:30 A.M.), during the postprandial phases (at 10:30 A.M., 2:30 P.M. and 8:30 P.M.) and during the postabsorptive periods (at 11:30 A.M. and 5:30 P.M.) in 66 patients with type 2 diabetes who were not being treated with prandial/premixed insulins or α-glucosidase inhibitors. The areas under the curve above the fasting BG concentrations (AUC1) and over 110 mg/dL (AUC2) were calculated for further evaluation of the correlations of the postprandial (AUC1) and fasting (AUC2 - AUC1) BG increments to the overall diurnal hyperglycemic status. Subjects were separated into two groups using the HbA1c cutoff value of 8%. The fasting BG was not correlated with the HbA1c in the group with HbA1c values of less than 8% ($r = 0.125$, $p = 0.473$). On the other hand, fasting hyperglycemia was strongly correlated with the HbA1c level in the group with HbA1c values of over 8.0% ($r = 0.406$, $p = 0.023$). Furthermore, postprandial hyperglycemia was strongly correlated with the HbA1c in the group with HbA1c levels less than 8.0% ($r = 0.524$, $p = 0.001$). Thus, there existed a progressive shift in the contribution of fasting and postprandial hyperglycemia to the overall hyperglycemic status with progression from moderate to severe diabetes mellitus in Japanese type 2 diabetic patients.

Key words: Fasting hyperglycemia, Postprandial hyperglycemia, Type 2 diabetes

ANTIDIABETIC AGENTS to treat diabetes mellitus are used based on their targeting fasting hyperglycemia, postprandial hyperglycemia, or both. Therefore, it is crucial to obtain a good grasp of a patient’s diurnal blood glucose profile. Postprandial hyperglycemia has been reported to be significantly correlated with the risk of microvascular and macrovascular complications [1, 2]. However, the exact contribution of postprandial glucose excursions to the overall glycermic status in Japanese patients with type 2 diabetes remains unknown. In this context, clinical biomarkers have been sought for predicting which might be the predominant abnormality contributing to diabetes mellitus in a given patient, postprandial blood glucose excursions or fasting blood glucose excursions. As it is difficult to conduct frequent measurements of the postprandial blood glucose levels, it would be ideal if the HbA1c could be measured as a marker of postprandial blood glucose.

Monnier reported that in patients with type 2 diabetes, there exists a progressive shift in the respective contributions of fasting and postprandial hyperglycemia to the overall hyperglycemic status with progression of diabetes mellitus from moderate to severe [3]. The contribution of postprandial glucose excursions appeared to be predominant in patients with moderate hyperglycemia, while that of fasting hyperglycemia appeared to increase with worsening of hyperglycemia.
from moderate to severe. These findings on the correlations between HbA1c and the fasting and postprandial hyperglycemia may be useful for judging whether a patient predominantly suffers from postprandial hyperglycemia or fasting hyperglycemia. However, to the best of our knowledge, there have been a few previous studies investigating the correlations between HbA1c and fasting and/or postprandial hyperglycemia in Japanese subjects [4, 5]. In these analyses, postprandial glycemic excursions were reported to be positively correlated with the HbA1c, however it remains unclear whether the correlation was limited to subjects with poor glycemic control or whether it was also valid in those with relatively good glycemic control, because the investigators did not provide any information on the correlation according to the HbA1c levels. This prompted us to investigate the correlations of fasting and postprandial hyperglycemia to the overall hyperglycemic status in relation to the severity of diabetes mellitus as assessed by measurement of the HbA1c value in Japanese patients with type 2 diabetes mellitus.

Research Design and Methods

Subjects
The subjects were a total of 66 patients (29 males, 37 females) with type 2 diabetes mellitus who were admitted to the Yokohama City University Hospital for diabetes education and blood glucose control between April 2006 and October 2008. The inclusion criteria were age between 30 and 81 years, body mass index (BMI) between 19.7 and 43.3, fasting plasma glucose (FPG) between 94 and 330 mg/dL, and HbA1c between 5.7 and 12.5%. As for the treatment taken by the subjects prior to the study, they had received either diet therapy alone, or had been treated with oral antidiabetic drugs (OADs) or basal insulin replacement therapy. Treatment with OADs was restricted to mono or combined therapy with metformin, pioglitazone and sulfonylurea, the dose of which had not been changed for at least 3 months prior to the study. Subjects who were treated with α-glucosidase inhibitors were excluded because of the distinct action of this class of drugs on postprandial glucose excursions. For the same reason, subjects who were receiving treatment with prandial and/or premixed insulins were also excluded.

Protocol of the study
This study was designed as a single-center, retrospective, observational study. After hospitalization, the subjects were placed on diet therapy. The energy content of the diet was determined taking into consideration the ideal body weight (IBW) and energy expenditure of each subject (25-30 kcal/IBW kg). The composition was approximately carbohydrate 60%, protein 20%, and fat 20%. Meals were given at 8:00 a.M., 12:00 P.M., and 6:00 P.M., and the calorie content was equally distributed among the three meals. On day 2 of admission, blood samples were collected from the patients after they had fasted overnight, for determination of the Hba1c. Diurnal blood glucose (BG) status was evaluated by self monitoring of blood glucose (SMBG) six times per day, as follows; in the fasting state (at 7:30 a.M.); during the postprandial phase (at 10:30 a.M., 2:30 P.M. and 8:30 P.M.); during the post-absorptive period (11:30 A.M. and 5:30 P.M.). Blood glucose was measured by Glutest Ace R (GT-1641).

Correlation of fasting blood glucose (FBG) and postprandial blood glucose (PBG) to the overall hyperglycemia status
The diurnal BG response to meals was estimated as a whole by calculating the incremental area under the daytime BG curve from 7:30 a.M. to 8:30 P.M. Two areas were calculated geometrically from the six-point curve, the area below the baseline level being ignored. First, the area under the curve (aUC1) above the FBG concentration was calculated above a baseline level equal to the FBG value, as a reflection of the postprandial glycemic responses to breakfast, lunch and dinner. Second, the AUC over 110 mg/dL (AUC2), was calculated above a baseline level equal to 110 mg/dL, as a reflection of the increase in both fasting and postprandial BG. We selected the baseline value of 110 mg/dL, because this threshold has been defined as the upper limit of normal BG in the fasting state by the Japan Diabetes Society [6]. Therefore, the difference (AUC2-AUC1) can be considered as an assessment of the increment in the FBG values.

Statistical analyses
Statistical analyses were conducted using the SPSS software, version 16J, for Windows. All results were expressed as means ± SD. All data, particularly those concerning the correlations of the FBG and PBG to the total glucose increments, were analyzed by determining Spearman’s correlation coefficients. The areas of FBG and PBG were compared using a paired t test.
Correlation analyses were performed using the least-squares method, and the strengths of the relationships were determined from the values of the coefficients of determination; \(p\)-values < 0.05 were considered to denote statistical significance. The relations between the areas and the whole Hba1c levels were analyzed by using locally weighted regression.

### Results

**Baseline characteristics and diurnal BG profiles**

The baseline characteristics of the entire subject population are shown in Table 1. Subjects were divided into two groups using the Hba1c cutoff level of 8%. The reasons were that Hba1c 8% is the cutoff point between fair control and poor control according to “Glycemic control indicators and assessment” [6] and that approximately equal number of subjects were assigned to each group (Group A, Hba1c < 8%, \(n = 35\); Group B, Hba1c \(\geq 8\%\), \(n = 31\)). It should also be noted that locally weighted regression analysis revealed that turning point existed at around Hba1c 8% (Fig. 1). This result validated our setting of cutoff point. Most subjects were over middle age and slightly overweight.
We next compared \( aUC_2 - aUC_1 \) and \( aUC_1 \) between the two groups. \( aUC_2 - aUC_1 \), which corresponds to the FBG area, was significantly larger in group B than in group A \( (p < 0.001) \). By contrast, \( aUC_1 \), which corresponds to the PBG area, was statistically indistinguishable between the two groups (Fig. 4).

**Correlational analysis between the AUCs and HbA1c**

In the entire subject group, both \( aUC_2 - aUC_1 \) and \( aUC_1 \) were positively correlated with the HbA1c (\( aUC_2 - aUC_1 \): \( r = 0.649, p < 0.001 \) and \( aUC_1 \): \( r = 0.386, p = 0.001 \)) (Fig. 5A, B). When examined by individual group, \( aUC_1 \) was correlated with the HbA1c \( (r = 0.524, p = 0.001) \), but not with \( aUC_2 - aUC_1 \) \( (r = 0.125, p = 0.473) \) in group A (Fig. 5C, D). By contrast, \( aUC_2 - aUC_1 \) was correlated with the HbA1c \( (r = 0.406, p = 0.023) \), but not with \( aUC_1 \) \( (r = 0.186, p = 0.316) \) in group B (Fig. 5E, F).

**Discussion**

The results of comparing \( aUC_2 - aUC_1 \) (a reflection of fasting glucose exposure) and \( aUC_1 \) (a reflection of postprandial exposure) between the two groups indicate that as the HbA1c increased, FBG also increased, whereas the postprandial glucose excursions were maintained fairly constant (Fig 4). This finding can be interpreted as fasting hyperglycemia being the predominant factor contributing to the overall diurnal hyperglycemia status in poorly controlled diabetic patients, whereas postprandial glucose elevations play the greater role in subjects with better glycemic control.

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As for the glycemic control status, group A showed fair control (HbA1c; 6.97 ± 0.70%) and group B showed insufficient control (HbA1c; 9.52 ± 1.17%). We calculated the C-peptide index (CPr index), according to the following equation: fasting C-peptide (ng/mL) divided by the fasting plasma glucose (mg/dL) × 100, as representing the endogenous basal insulin secretory capacity [7]. The CPr index was fairly well maintained in both groups. Thus, no significant differences in the age, BMI or endogenous insulin secretory capacity were seen between the two groups.

As for prior therapy, 51.5% of the subjects were being treated with OADs. There was significantly larger number of patients under treatment with metformin or pioglitazone in group B than in group A, while a significantly larger number of subjects were on diet and exercise therapy alone in group A than in group B.

The six-time-point diurnal profiles of BG in group A and group B are shown in Fig. 2. The pre-lunch blood glucose level did not return to the FBG values.

**Correlational analyses between the HbA1c values and six-time-point blood glucose profiles in the entire subject population, in group A and B**

In the entire subject group, the BG was positively correlated with the HbA1c at all the time-points. Fasting glucose (7:30 A.M.) was correlated with the HbA1c in group B \( (r = 0.564, p < 0.001) \), but not in group A \( (r = 0.155, p = 0.473) \) (Fig. 3). The correlation coefficients between the HbA1c and postprandial BG (10:30 A.M., 2:30 P.M., 8:30 P.M.) were larger in group A than in group B.
Fig. 3. Correlational analyses between HbA1c and six-time-point diurnal blood glucose profile in the entire subject group, in group A and B

In the entire subject group, the blood glucose was positively correlated with the HbA1c at all the time-points ($r = 0.576-0.688, p < 0.05$). In group A, the fasting glucose (7:30 A.M.) was not correlated with the HbA1c ($r = 0.155, p = 0.473$), whereas the blood glucose levels at other time-points were correlated with the HbA1c ($r = 0.355-0.698, p < 0.05$). In group B, the blood glucose levels at all the time-points of measurements were positively correlated with the HbA1c ($r = 0.356-0.588, p < 0.05$). The correlation coefficient between the levels in the postprandial phase (10:30 A.M., 2:30 P.M., 8:30 P.M.) and HbA1c were larger in group A than in group B.
Fig. 4. Comparison of AUC2-AUC1 and AUC1 between the two groups
Open squares (□): AUC2-AUC1 (FBG area); closed squares (■): AUC1 (PBG area).

Fig. 5. Correlational analyses between HbA1c and AUC2-AUC1, AUC1 in the entire subject group, in group A and B
In the entire subject group, both AUC2-AUC1 (FBG area) (A) and AUC1 (PBG area) (B) were positively correlated with the HbA1c ($r = 0.649$, $p < 0.001$ and $r = 0.366$, $p = 0.001$, respectively). In group A, AUC1 (PBG area) (D) was correlated with the HbA1c ($r = 0.524$, $p = 0.001$), but not with AUC2-AUC1 (FBG area) (C) ($r = 0.125$, $p = 0.473$). In group B, AUC2-AUC1 (FBG area) (E) was correlated with the HbA1c ($r = 0.406$, $p = 0.023$), but not with AUC1 (PBG area) (F) ($r = 0.186$, $p = 0.316$).
poorly controlled diabetes. These results are compatible with previous reports from foreign countries [3, 8] as well as from Japan [4, 5]. In the aforementioned Japanese reports [4, 5], the postprandial glycemic excursions were reported to be positively correlated with the HbA1c, however, it remained unclear whether the validity of this correlation was limited to subjects with poor glycemic control or whether it also applied to patients with relatively fair glycemic control.

Deleterious effect of excessive postprandial glycemic excursion on macroangiopathy in well controlled diabetes is strongly suggested [9, 10]. By contrast, fasting hyperglycemia plays the predominant role if the HbA1c level rises above 8.0%. This finding is related mainly to the fact that while AUC2-AUC1 increased as the diabetes control worsened, AUC1 remained stable. Such an observation can explain the specific deleterious effect of postprandial hyperglycemia reported in the subset of patients with poorly controlled type 2 diabetes included in previous studies [1, 10]. All of these interpretations are tenable, provided that the validity of the observations of the six–time-point diurnal glucose profile under standard conditions with standardized meals in a specific study can be extrapolated to chronic variations of the blood glucose levels in real life. The answer to refute all these possible limitations lies in the finding of significant correlations between the areas under the six-time-point diurnal glucose profiles and the HbA1c values.

Consistent with Monnier’s report [3], our results indicate that there is a progressive shift in the contributions of fasting and postprandial hyperglycemia to the overall hyperglycemic status with worsening of hyperglycemia from moderate to severe, the effects of postprandial glucose excursions being predominant in patients with moderate hyperglycemia, and fasting hyperglycemia playing an increasingly predominant role with worsening of hyperglycemia. In U.K. Prospective Diabetes Study [11], microvascular risk and emergent risk reductions for myocardial infarction and death from any cause were reduced by keeping HbA1c better during 10 years. Measurements of HbA1c may provide useful information to determine which glycemic component, fasting or postprandial hyperglycemia, might be responsible for the overall glycemic abnormality in a given patient.

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References
