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NOTE

Contribution of Fasting and Postprandial Hyperglycemia to Hemoglobin A_{1c} in Insulin-Treated Japanese Diabetic Patients

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Abstract. The contribution of fasting and postprandial glucose to hemoglobin A_{1c} (HbA_{1c}) levels was evaluated in insulin-treated patients. In 57 insulin-treated, diabetic out-patients, fasting glucose (before breakfast (B-FG), lunch (L-FG) and dinner (D-FG)) and postprandial glucose (B-PPG, L-PPG and D-PPG) levels were determined by the patients themselves at home using glucose self-monitoring apparatus over the course of one week. The correlation between HbA_{1c} levels and self monitored blood glucose levels were calculated. In the conventionally treated group, there was a significant correlation between HbA_{1c} and fasting glucose (FG) levels only before lunch, but at 2 hr after (PPG) all meals. In the intensively treated group, a significant correlation between HbA_{1c} levels and FG levels was found before lunch and at 2 hr after breakfast and dinner. In all subjects, only FG levels before lunch correlated significantly with HbA_{1c} levels, although PPG levels were significantly correlated with HbA_{1c} at all points. The correlation was highest with PPG after breakfast and dinner. The sum of all FG, PPG and FG + PPG levels was significantly correlated with HbA_{1c} levels. Postprandial hyperglycemia after breakfast and dinner should be regarded as most important for improving HbA_{1c} levels in insulin treated diabetic patients.

Key words: Hemoglobin A_{1c}, Insulin, Postprandial hyperglycemia, Diabetes mellitus

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GLYCEMIC control is important in the prevention of diabetic complications in type 1 and type 2 diabetic patients [1, 2]. Hemoglobin A_{1c} (HbA_{1c}) level is widely used as a marker of glycemic control. However, the relation of HbA_{1c} levels to diurnal excursion of blood glucose levels still remains to be clearly elucidated in diabetic subjects, since the relative contribution of postprandial glucose levels might be influenced by circumstances and subjects [3]. HbA_{1c} levels correlated more strongly with fasting plasma glucose levels than with the overall postprandial glucose exposure measured by a standardized meal test in newly diagnosed treatment-naïve subjects with type 2 diabetes mellitus [4]. The relative contribution of postprandial glucose levels decreased progressively from the lowest to the highest quintile of HbA_{1c} levels, whereas the relative contribution of fasting glucose levels increased gradually with increasing levels of HbA_{1c} in non-insulin- and non-acarbose-treated diabetic subjects [5, 6]. While the HbA_{1c} level was more closely related to postprandial glucose levels in non-insulin-treated type 2 diabetic subjects [4], the exact contribution of fasting and postprandial glucose to HbA_{1c} levels remains unclear in insulin-treated patients. We analyzed the contribution of diurnal glycemic profiles to HbA_{1c} levels in diabetic patients treated with insulin.

Fifty-seven insulin-treated, diabetic out-patients were recruited for this study. The number of patients treated with insulin twice a day (b.i.d.) was 24 (type 1 diabetes; 1, type 2 diabetes; 23), and the number intensively treated (basal-bolus) was 33 (type 1 diabetes; 14, type 2 diabetes; 19). Eligibility for the study was based on a diagnosis of diabetes for at least 12 months. In these patients, changes of the insulin dose used were maintained within 10% of total daily insulin dosage for at

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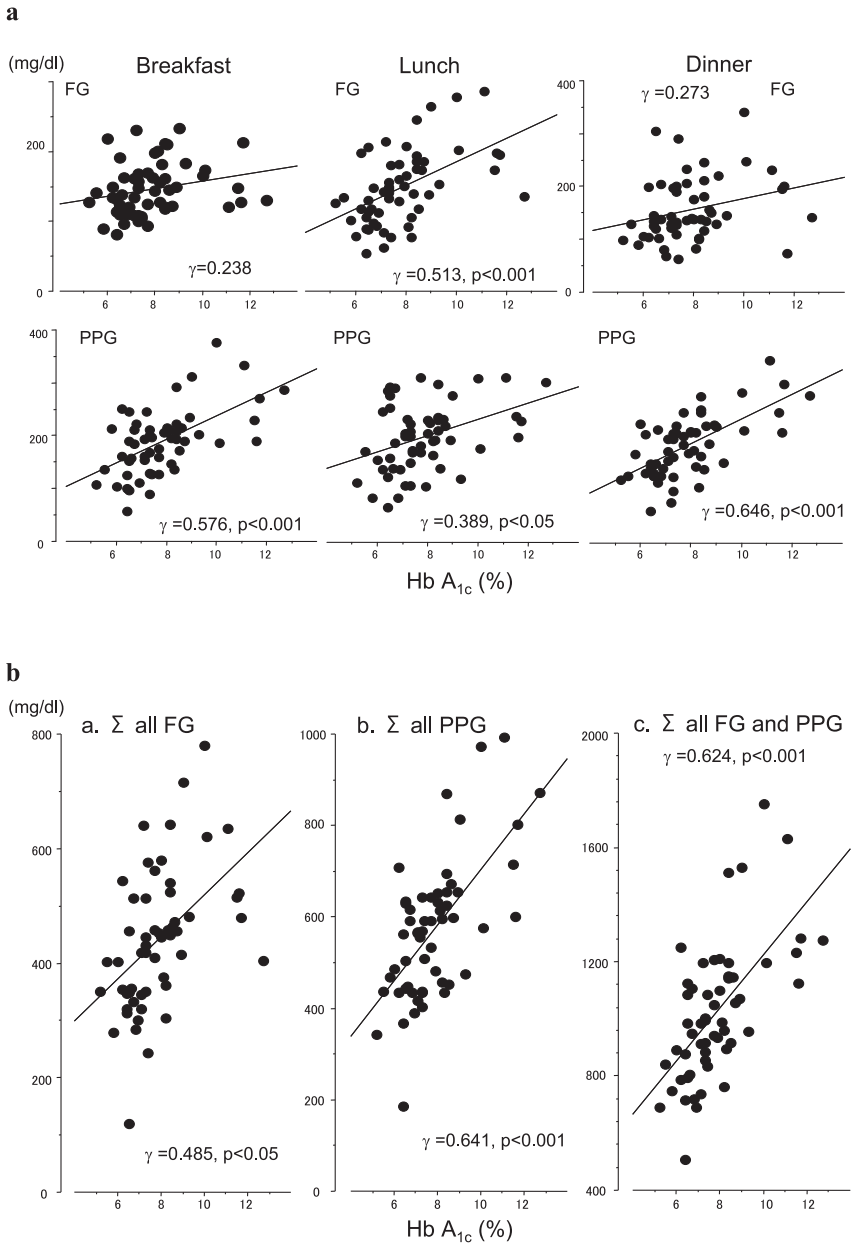

Fig. 1. Correlation of Hb A_{1c} levels to fasting (FG) and postprandial glucose (PPG) levels (a), and the sum of all FG, all PPG, and total of all FG + all PPG levels (b) in diabetic patients.

least 8 weeks before the start of the study. Diet and life-style were also not changed within the 3 months before the study. Fasting glucose (before breakfast (B-FG), lunch (L-FG) and dinner (D-FG)) and postprandial glucose (B-PPG, L-PPG and D-PPG) levels were measured by the patients themselves at home using glucose self-monitoring apparatus over the week before their visit to our hospital. HbA_{1c} levels were measured by HPLC on the visit to our hospital. The correlation of HbA_{1c} levels to self monitored blood glucose levels was calculated for each measurement point and the sum of blood glucose levels and the strengths of the relationships are given by coefficients of determination (γ^2).

The average HbA_{1c} levels in all subjects was 7.83%. In the patients treated with conventional insulin administration (b.i.d.), L-FG and all PPG levels correlated significantly with HbA_{1c} levels and the correlations

Table 1. Clinical background of the patients

	b.i.d.	IIT
age	60.7 ± 3.3	46.4 ± 2.9
M/F	7/17	6/27
BMI (kg/m^2)	24.0 ± 0.8	25.2 ± 1.0
Total Insulin Dose (U/day)	30.4 ± 2.5	41.1 ± 3.3
Patients Receiving Fast-Acting Insulin (%)	33.3	45.5
HbA_{1c} (%)	7.71 ± 0.38	7.92 ± 0.26
B-FG (mg/dl)	135.5 ± 6.0	153.6 ± 7.3
B-PPG (mg/dl)	174.1 ± 11.6	200.3 ± 11.3
L-FG (mg/dl)	125.8 ± 10.2	161.0 ± 8.7
L-PPG (mg/dl)	192.6 ± 12.9	204.2 ± 11.6
D-FG (mg/dl)	139.7 ± 10.4	166.8 ± 11.2
D-PPG (mg/dl)	176.6 ± 11.9	188.7 ± 10.2

b.i.d.: twice a day, IIT: intensive insulin therapy, M: male, F: female, BMI: body mass index, Fast Acting Insulin: fast-acting insulin or premixed insulin with fast- acting insulin

of B-PPG ($\gamma = 0.669$) and D-PPG ($\gamma = 0.707$) were highly significant ($p<0.001$). On the other hand, B-FG, L-FG, B-PPG and D-PPG levels correlated significantly with HbA_{1c} levels in basal-bolus-insulin-treated patients and the correlations of B-PPG ($\gamma = 0.525$) and D-PPG ($\gamma = 0.602$) levels were highly significant ($p<0.01$). Blood glucose excursion in the morning therefore appears to be associated with HbA_{1c} levels in patients receiving intensive insulin treatment.

We analyzed the correlation between blood glucose and HbA_{1c} levels in all patients included in the study (Fig. 1a). There was no significant correlation between HbA_{1c} levels and B-FG or D-FG levels and only L-FG levels were significantly correlated with HbA_{1c} levels ($\gamma = 0.513$, $p<0.001$). In contrast, all PPG levels were significantly correlated with HbA_{1c} levels (B-PPG; $\gamma = 0.576$, $p<0.001$), L-PPG; ($\gamma = 0.386$, $p<0.05$) and D-PPG; $\gamma = 0.650$, $p<0.001$) and the correlation with D-PPG was highest. The sum of all FG and PPG levels was calculated (Fig. 1b). The correlation of the sum of all PPG (B-PPG, L-PPG, D-PPG) levels to HbA_{1c} levels ($\gamma = 0.641$, $p<0.001$) was higher than the correlation of the sum of all FG levels (B-FG, L-FG, D-FG) to HbA_{1c} levels ($\gamma = 0.485$, $p<0.05$). The total of all FG and PPG levels was also significantly correlated with HbA_{1c} levels ($\gamma = 0.624$, $p<0.001$). Furthermore, we divided all patients into two groups (HbA_{1c} >7.5% and ≤7.5%) to examine the contribution of blood glucose to HbA_{1c} levels. In the group with HbA_{1c} ≤7.5%, there was no significant correlation between HbA_{1c} and blood glucose level at each point. In contrast, a significant correlation was found between HbA_{1c} and B-PPG ($\gamma = 0.508$, $p<0.01$) and D-PPG ($\gamma = 0.541$, $p<0.01$) in the group with HbA_{1c} >7.5%. We also examined the difference in the contribution between the types of diabetes. In type 1 diabetic patients (n = 15), all PPG levels correlated significantly with HbA_{1c}, while there was no correlation with FG levels at all. In type 2 diabetic patients (n = 42), B-FG, B-PPG, L-FG and D-PPG were all significantly correlated with HbA_{1c}.

The finding that both B-PPG and D-PPG levels are highly correlated with HbA_{1c} levels in insulin-treated, diabetic out-patients, especially poorly-controlled patients, but only L-FG glucose levels correlated significantly with HbA_{1c} levels, indicate that PPG levels should be considered a more important determinant of HbA_{1c} levels than FG levels in insulin-treated diabetic patients, and that blood glucose excursion in the morning could be an important determinant of HbA_{1c} levels in both type 1 and type 2 diabetic patients treated with insulin. Fasting glucose level is an important factor, which determines HbA_{1c} levels in newly diagnosed, treatment-naïve, type 2 diabetic patients [4]. However postprandial glucose levels appear to contribute to HbA_{1c} levels in diabetic patients treated with sulfonylurea or by di*et al*one who show fairly good glycemic control [5, 6]. The present data raise the possibility that PPG could contribute more to HbA_{1c} levels than FG in insulin-treated diabetic patients. Reduction of postprandial hyperglycemia by the addition of a fast-acting insulin component has been shown to be beneficial to the improvement of HbA_{1c} levels in type 2 diabetes [7, 8]. It is suggested that improvement of PPG levels should be indispensable in normalizing HbA_{1c} levels in diabetic patients treated with insulin.

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