Note

Contribution of Fasting and Postprandial Hyperglycemia to Hemoglobin A₁c in Insulin-Treated Japanese Diabetic Patients

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Abstract. The contribution of fasting and postprandial glucose to hemoglobin A₁c (HbA₁c) 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 HbA₁c levels and self monitored blood glucose levels were calculated. In the conventionally treated group, there was a significant correlation between HbA₁c 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 HbA₁c 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 HbA₁c levels, although PPG levels were significantly correlated with HbA₁c 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 HbA₁c levels. Postprandial hyperglycemia after breakfast and dinner should be regarded as most important for improving HbA₁c levels in insulin treated diabetic patients.

Key words: Hemoglobin A₁c, Insulin, Postprandial hyperglycemia, Diabetes mellitus

GLYCEMIC control is important in the prevention of diabetic complications in type 1 and type 2 diabetic patients [1, 2]. Hemoglobin A₁c (HbA₁c) level is widely used as a marker of glycemic control. However, the relation of HbA₁c 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]. HbA₁c 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 HbA₁c levels, whereas the relative contribution of fasting glucose levels increased gradually with increasing levels of HbA₁c in non-insulin- and non-acarbose-treated diabetic subjects [5, 6]. While the HbA₁c 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 HbA₁c levels remains unclear in insulin-treated patients. We analyzed the contribution of diurnal glycemic profiles to HbA₁c 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
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 ($\gamma^2$).

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
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 ($\gamma = 0.602$) 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 diet alone 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.

**References**


