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The Relationship between Plasma Glucose Concentration and Hemoglobin A1c during a Standardized Meal Tolerance Test in Individualss with Type 2 Diabetes

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Background: The aims of this study were to assess plasma glucose concentration and the extent of excursion during a standardized meal tolerance test (MTT), and to evaluate the relationship between glycosylated hemoglobin (HbA1c) and plasma glucose concentration at different times of the day in patients with type 2 diabetes. **Methods:** One hundred seventy-two patients (age, 57.3±0.8 years; HbA1c, 7.8%±0.1%) with type 2 diabetes were assigned to receive a standardized MTT after a 10-hour overnight fast. Meals were provided at 8:00 A.M. and 12:00 P.M. Plasma glucose concentration was determined at 8:00 A.M. (before breakfast) and then at hourly intervals until 4:00 P.M. HbA1c concentrations were determined in all patients. **Results:** HbA1c level correlated significantly with daily plasma glucose concentration during the standardized MTT (r = 0.49-0.71; all $P < 0.001$). The correlation coefficient was higher after lunch (r = 0.517, P < 0.001) than before lunch (r = 0.175, $P = 0.025$) in patients with type 2 diabetes. In patients with HbA1c < 7.0%, the correlation between HbA1c and the incremental area under the curve (IAUC) was higher before lunch (r = 0.408, $P = 0.004$) than after lunch (r = 0.259, $P = 0.090$). In contrast, in patients with HbA1c > 8%, the correlation between IAUC and HbA1c was stronger after lunch (r = 0.465, $P = 0.001$) than before lunch (r = -0.230, $P = 0.074$). **Conclusions:** In general, HbA1c level correlated significantly with daily plasma glucose concentration during a standardized MTT in patients with type 2 diabetes; the correlation was stronger after lunch than before lunch. The plasma glucose response to a meal correlated with HbA1c better before lunch in patients with HbA1c < 7.0%, whereas the correlation was stronger after lunch in patients with poor glucose control and HbA1c > 8.0%.

Key words: fasting plasma glucose, postprandial plasma glucose, HbA1c, type 2 diabetes, standardized meal tolerance test

INTRODUCTION

Type 2 diabetes is the most common form of diabetes mellitus, accounting for about 95% of all cases diagnosed. Based on estimates of future population growth, it has been suggested that as many as 200-300 million worldwide will develop type 2 diabetes by the year 2025[1]. Recent epidemiological studies have shown that type 2 diabetes is a major cause of morbidity and premature death, affecting 100 million people throughout the world[2-4].

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Hyperglycemia is a major independent risk factor for the development of microvascular and macrovascular disease in type 2 diabetic patients[5-7]. Several major studies, including the Diabetes Control and Complications Trial (DCCT)[8] and the UK Prospective Diabetes Study (UKPDS)[9], have shown a strong relationship between glycemic control and microvascular and neuropathic complications. Atherosclerotic cardiovascular disease also increases as the degree of hyperglycemia worsens[10]. Traditionally, the management of patients with type 2 diabetes has been aimed at controlling fasting plasma glucose concentration and glycosylated hemoglobin (HbA1c) level. However, some studies have recently reported that postprandial glucose concentration is a better predictor of HbA1c than the fasting value[11-13]. Therefore, in patients with an elevated HbA1c, the postprandial plasma glucose concentration may play a disproportionate role in the genesis of both the microvascular and macrovascular complications that accompany uncontrolled diabetes[14-16]. Some studies have

also suggested that postprandial blood glucose concentration contributes as an independent factor associated with the outcome of cardiovascular morbidity or mortality in diabetic and nondiabetic patients[17-19]. For example, analysis of the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study showed that abnormalities in two-hour glucose concentration were better predictors of all-cause mortality than fasting glucose concentration alone[20]. Hyperglycemia may induce the pathogenesis of cardiovascular complications through various mechanisms. The key pathogenic mechanisms include overproduction of superoxide ion and an imbalance between free radical production and antioxidant defenses[21-22]. Increasing oxidative stress coupled with consumption of antioxidant defenses has also been confirmed during the postprandial state in patients with type 2 diabetes[14].

Earlier investigations examining the relationship between HbA1c and plasma glucose concentration at different times of the day have yielded varied conclusions. Some studies have shown that HbA1c has a stronger association with fasting glucose concentration[23-24], but others have not[11-12]. To optimize glycemic control, it is essential to use appropriate therapy aimed at reducing fasting or postprandial glucose concentrations based on the overall HbA1c. The goals of our study were to evaluate the plasma glucose concentration at different times of the day during a standardized meal tolerance test (MTT) and the relationship between plasma glucose concentration and HbA1c in patients with type 2 diabetes.

METHODS

Our patients were randomly recruited from outpatient clinics at Taichung Veterans General Hospital and Tri-Service General Hospital. One hundred seventy-two patients with type 2 diabetes between the ages of 35 and 75 years and in otherwise good general health without a history of renal, liver, cardiovascular, or endocrine diseases were enrolled in the study.

All patients were assigned to receive a standardized MTT after a 10-hour overnight fast. Blood was obtained at 8:00 A.M. (before breakfast) and then at hourly intervals until 4:00 P.M. to determine the plasma glucose concentration. The standardized MTT meals were isocaloric (30 kcal/kg), and each meal contained (as a percentage of the total energy) 15% protein, 33% fat, and 52% carbohydrate. The meals were provided at 8:00 A.M. and 12:00 P.M. and had 20% and 40% of the daily total caloric intake, respectively. The HbA1c level was determined in each blood sample in all patients.

Plasma glucose concentration was determined by the glucose oxidase method on a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA, USA). HbA1c was measured using a Bio-Rad Variant II automatic analyzer (Bio-Rad Diagnostic Group, Los Angeles, CA, USA). The intra-assay and interassay coefficients of variance for HbA1c were 1.9% and 3.7%, respectively. The incremental area under the curve (IAUC) of plasma glucose after a meal was defined as the area under the glucose concentration curve above the fasting value.

All descriptive data are expressed as the mean Ñb standard error (SE). In addition, Pearson correlation coefficient analysis was used to examine the relationship between the various hourly plasma glucose concentrations and HbA1c after the meals. Statistical analysis was carried out using SPSS version 10.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 172 patients, 84 men and 88 women, with an average diagnosed duration of type 2 diabetes of 3.9±0.4 years, participated in the study. They were divided into three groups according to the HbA1c (< 7.0%, 7.0-8.0%, > 8.0%); the clinical characteristics are shown in Table 1. All participants were being treated with diet, pioglitazone, sulfonylureas, metformin, or a combination of sulfonylureas and metformin (Table 1).

Table 1 Clinical and metabolic characteristics (mean±SE) of patients

	All	Group 1 HbA1c < 7%	Group 2 HbA1c 7-8%	Group 3 HbA1c > 8%
Number	172	51	59	62
Age (years)	57.3±0.8	59.6±1.5	58.3±1.5	54.4 ±1.4
Sex (M/F)	84/88	23/28	30/29	31/31
BMI (kg/m^2)	26.2±0.3	26.3±0.5	26.7±0.4	25.7±0.4
Duration of diabetes (years)	3.9±0.4	4.9±0.7	5.0±0.8	1.9±0.6
HbA1c (%)	7.8±0.1	6.0±0.1	7.5±0.1	9.6±0.2
Diet control	35 (20.3%)	4 (7.8%)	7 (11.9%)	24 (38.8%)
Pioglitazone	12 (7.0%)	0 (0%)	3 (5.1%)	9 (14.5%)
Metformin	15 (8.7%)	3 (5.9%)	7 (11.9%)	5 (8.1%)
Sulfonylureas	65 (37.8%)	25 (49.0%)	20 (33.9%)	20 (32.2%)
Metformin + sulfonylureas	45 (26.2%)	19 (37.3%)	22 (37.3%)	4 (6.4%)
TAUC in plasma glucose under MTT (mg.hr/dl)	1715±35	1449±36*	1594±42*	2046± 62*
IAUC in plasma glucose under MTT (mg.hr/dl)	396±18	301±24†	384±29†	524± 28†

*P < 0.01 Group 1 vs. Group 2 vs. Group 3; †P < 0.01 Group 1 vs. Group 2 vs. Group 3. BMI, body mass index; TAUC, the total area under the curve; MTT, meal tolerance test; IAUC, the incremental area under the curve.

Table 2 Pearson's correlations between ambient plasma glucose concentration and HbA1c

		HbA1c	
	Concentration	r	*p*
Fasting PG (8 A.M.) (mg/dl)	164.8±3.2	0.624	< 0.001
1 h PG (9 A.M.) (mg/dl)	244.9±4.5	0.574	< 0.001
2 h PG (10 A.M.) (mg/dl)	242.9±4.8	0.492	< 0.001
3 h PG (11 A.M.) (mg/dl)	198.5±5.0	0.499	< 0.001
4 h PG (12 A.M.) (mg/dl)	159.8±4.7	0.531	< 0.001
5 h PG (1 P.M.) (mg/dl)	221.7±4.7	0.637	< 0.001
6 h PG (2 P.M.) (mg/dl)	231.6±5.4	0.678	< 0.001
7 h PG (3 P.M.) (mg/dl)	226.3±5.4	0.709	< 0.001
8 h PG (4 P.M.) (mg/dl)	211.0±5.5	0.644	< 0.001
TAUC in plasma glucose under MTT(mg.hr/dl)	1715 ±35	0.663	< 0.001
MIAUC in plasma glucose under MTT(mg.hr/dl)	190 ±9	0.175	0.025
AIAUC in plasma glucose under MTT(mg.hr/dl)	205 ±12	0.517	< 0.001

PG, plasma glucose; TAUC, the total area under the curve; MTT, meal tolerance test; MIAUC, the incremental area under the curve during the morning period; AIAUC, the incremental area under the curve during the afternoon period. Values are expressed as mean ± SE.

Table 2 shows the Pearson's correlations between the ambient plasma glucose concentrations at different times and HbA1c. All of these correlations were significant. However, the stronger correlations were generally noted after lunch (r = 0.64-0.71) than before lunch (r = 0.49-0.62). The correlations between the IAUC of plasma glucose responses and HbA1c were also highly significant. To further evaluate the relationships between IAUC and HbA1c at different times, we divided the eight-hour MTT into morning and afternoon periods, and calculated the IAUC separately to give a morning IAUC (MIAUC) and afternoon IAUC (AIAUC). Although both the MIAUC and AIAUC correlated significantly with HbA1c, the correlation coefficients were higher for the AIAUC than for the MIAUC.

Table 3 illustrates the correlations between HbA1c and ambient plasma glucose concentration in the three groups classified according to HbA1c. In the group with good glycemic control (HbA1c < 7.0%), significant correlations between HbA1c and plasma glucose concentration were noted three and four hours after breakfast and one hour after lunch. These observations were also compatible with the correlation between HbA1c and MIAUC, but not between HbA1c and AIAUC. In the group with fair glycemic control (HbA1c 7.0-8.0%), HbA1c and plasma glucose concentration correlated significantly only two hours after breakfast. In those with poor control (HbA1c > 8.0%), HbA1c and plasma glucose concentration correlated significantly over the entire eight hours, but the correlations were stronger before breakfast and during the afternoon than during the morning.

Table 3 Pearson's correlations between ambient plasma glucose concentration and HbA1c in patients grouped according to HbA1c

	Group 1 HbA1c < 7.0% (n=51)			Group 2 HbA1c=7~8% (n=59)			Group 3 HbA1c > 8% (n=62)		
	Concentration	r	*p*	Concentration	r	*p*	Concentration	r	*p*
Fasting PG (mg/dl)	143.7±3.5	0.122	NS	154.5±4.0	0.165	NS	192.9±6.1	0.595	< 0.001
1 h PG (9 A.M.) (mg/dl)	213.7±6.1	0.082	NS	230.1±5.4	0.159	NS	285.8±8.0	0.424	0.001
2 h PG (10 A.M.) (mg/dl)	216.9±6.8	0.218	NS	225.4±6.8	0.276	0.034	281.3±8.1	0.290	0.022
3 h PG (11 A.M.) (mg/dl)	170.8±6.5	0.380	0.006	182.1±7.0	0.228	NS	237.7±8.4	0.258	0.043
4 h PG (12 A.M.) (mg/dl)	130.0±5.1	0.344	0.016	145.5±5.4	0.112	NS	199.0±8.7	0.315	0.012
5 h PG (1 P.M.) (mg/dl)	185.2±5.2	0.295	0.035	212.9±6.3	0.085	NS	260.8±8.7	0.599	< 0.001
6 h PG (2 P.M.) (mg/dl)	190.0±6.1	0.207	NS	14.1±6.7	0.066	NS	283.3±9.5	0.640	< 0.001
7 h PG (3 P.M.) (mg/dl)	181.6±5.8	-0.006	NS	210.1±6.1	0.117	NS	280.0±9.6	0.711	< 0.001
8 h PG (4 P.M.) (mg/dl)	166.4±5.7	0.035	NS	00.1±7.4	0.051	NS	257.4±9.7	0.673	< 0.001
TAUC in plasma glucose under MTT (mg.hr/dl)	1448 ±36	0.255	NS	1594 ±315	0.159	NS	2046 ±62	0.549	< 0.001
MIAUC in plasma glucose under MTT (mg.hr/dl)	164 ±14	0.408	0.004	70 ±15	0.126	NS	29 ±16	-0.230	NS
AIAUC in plasma glucose under MTT (mg.hr/dl)	127 ±16	0.259	NS	192 ±18	0.096	NS	281 ±12	0.465	0.001

PG, plasma glucose; TAUC, the total area under the curve; MTT, meal tolerance test; MIAUC, the incremental area under the curve during the morning period; AIAUC, the incremental area under the curve during the afternoon period. NS, not significant. Values are expressed as mean ± SE.

DISCUSSION

Although healthcare professionals have traditionally been advised to focus on HbA1c and fasting plasma glucose concentration as the indicators for monitoring glycemic control in patients with type 2 diabetes, increasing evidence now implicates postprandial glycemia as an independent risk factor for cardiovascular disease[20,25]. We observed a significant correlation between HbA1c and the total area under the curve, MIAUC, AIAUC, and the plasma glucose concentration at different times during the MTT. In general, HbA1c correlated more strongly with the plasma glucose concentration at different times after than before lunch.

In most large studies, the authors evaluated either postglucose-challenged or postmeal-challenged blood glucose concentrations. Avignon et al.[12] evaluated the plasma glucose concentration at different times throughout the day in patients with type 2 diabetes and concluded that postlunch and extended postlunch glucose concentrations are better predictors of HbA1c than is the fasting glucose concentration[12]. Bonora et al.[26] assessed the extent of plasma glucose excursions with meals and the relationship between plasma glucose concentration at different times of the day; they found that HbA1c is more highly correlated with preprandial than with postprandial plasma or blood glucose concentration. Despite the significant correlations between HbA1c and plasma glucose concentration at different times during the day in these studies, their conclusions differed. This discrepancy may result from the different glycemic status of the subjects in the two studies.

Our findings are similar to those of Woerle et al.[27], who found that, in response to an oral glucose tolerance test, the change in two-hour postprandial glucose concentration was much greater than the change in fasting plasma glucose concentration for every unit increase in HbA1c in individuals with an HbA1c < 7.0%, indicating that postprandial glucose contributes more than fasting glucose to HbA1c in patients with diabetes. Monnier et al.[28] also showed that the contribution of postprandial glucose is predominant in well controlled and reasonably well controlled patients but decreases as glycemic control deteriorates (HbA1c < 7.3% in about 70% and HbA1c > 10.2% in about 30% of their patients). In addition, our data showed stronger correlations between HbA1c and the prelunch glucose concentration, and between HbA1c and glucose excursions before lunch in individuals with HbA1c < 7.0%. Similar to the findings of Monnier et al.[28], we found that, in our patients with better control (HbA1c < 7.0%), lowering the postprandial glucose concentration, especially the prelunch value, achieved the greatest reduction in HbA1c. In patients with fair control (HbA1c 7-8%), we found a significant correlation between HbA1c and ambient plasma glucose concentration only two hours after breakfast. A report by Peter et al.[29] indicated that the strong correlation between HbA1c and plasma glucose concentration in all postprandial periods is expected in patients with fair control (HbA1c 7-8%). These discrepancies may be caused by concurrent oral hypoglycemic agents taken by most of our patients (88.1%), whereas those in the study of Peter et al. were newly diagnosed, treatment-naive patients with type 2 diabetes. Nevertheless, our findings suggest that the plasma glucose concentration two hours after breakfast rather than during fasting should be the main target of treatment in these individuals.

We also observed persistent good correlations between HbA1c and ambient plasma glucose concentrations during fasting and before and after lunch in poorly controlled patients (HbA1c > 8.0%). Our findings are compatible with a recent report by Monnier et al.[30] showing that the deterioration of glucose homeostasis in patients with type 2 diabetes progresses from postprandial to persistent fasting hyperglycemia through a three-step process. We also found that the significant correlation between HbA1c and fasting glucose concentration occurred only in the poor control group (HbA1c > 8%, Table 3). These observations are consistent with those in a previous report[28] showing that the contribution of fasting hyperglycemia to excess hyperglycemia increases as glycemic control deteriorates. In addition, we also observed in the poor glycemic control group that the correlation between HbA1c and plasma glucose concentration is higher in the afternoon than in the morning. This finding is similar to that of Avignon et al.[12] who demonstrated that in the poorly controlled patients with type 2 diabetes (HbA1c > 8.5%), the postlunch rather than prelunch plasma glucose concentration is a better predictor of glycemic control. This implies that prelunch glucose excursion may reflect only the pathophysiological process of type 2 diabetes before lunch, whereas postlunch glucose excursion reflects the overall pathophysiological process from the morning to afternoon. In addition, in nondiabetic patients, the insulin response to glucose loads is delayed in the afternoon and is lower than in the morning[31]. Thus, it is likely that, in type 2 diabetes, insulin secretion decreases from morning to afternoon; if so, this would account for the progressive increase in the postlunch glucose excursion and the correlation between HbA1c and plasma glucose concentration.

Our observation is relevant to personalized blood glucose lowering therapy in patients with type 2 diabetes. For

patients with HbA1c < 7.0%, the primary therapeutic goal should be to correct postbreakfast and postlunch hyperglycemia to achieve HbA1c as close to normal as possible (i.e., < 6%). For patients with HbA1c between 7% and 8%, the two-hour postbreakfast rather than the fasting glucose concentration should be the primary therapeutic goal. Thus, administration of rapid-acting insulin-secreting agents or rapid-acting insulin analogues before breakfast could be considered with the aim of achieving HbA1c < 7.0%, the recommended target of the American Diabetes Association[32]. Finally, in patients with poor glycemic control (HbA1c > 8%), the therapeutic requirement is first to correct the fasting hyperglycemia using metformin or long-acting insulin analogues given before dinner or at bedtime. Moreover, preprandial administration of rapid-acting insulin-secreting agents or of rapid-acting insulin analogues should be added to correct postprandial hyperglycemia, especially for postlunch glucose excursions, to further improve glycemic control or to achieve near normoglycemia.

Our study has several limitations. We divided our study population into three groups with good, fair, and poor control based on their HbA1c values. This classification led to a wider range of HbA1c in the poor-control group, and a wider range of HbA1c is more likely to reach significance in statistical analysis. Many of these patients (80%) were on various oral hypoglycemic agents, and the effects of these agents on the daily glucose responses are not easily measured.

In conclusion, although the relationship between the 'glucose triad' of HbA1c and fasting and postprandial plasma glucose concentrations is complex, it is important for both patients and healthcare providers to understand the relationship between each component of the triad in setting proper glycemic goals to prevent the complications of diabetes. We demonstrated that HbA1c correlates significantly with daily plasma glucose concentration during a standardized MTT and that these variables are more highly correlated after lunch than before lunch in patients with type 2 diabetes. In patients with good and fair glycemic control, lowering the postprandial glucose concentration is likely to achieve the greatest reduction in HbA1c. On the other hand, in poorly controlled patients (HbA1c > 8%), the primary goal of therapy should be to correct both fasting and postprandial hyperglycemia. Therefore, the clinician should consider the HbA1c values according to the pathophysiological status of diabetes in striving for the optimal treatment.

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