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Carbohydrate Intake Is Correlated with the Glycated Albumin to Glycated Hemoglobin Ratio in Drug-Naive Patients with Type 2 Diabetes

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Abstract

***Background*: The glycated albumin (GA) to HbA1c ratio (GA/HbA1c ratio) has been reported to reflect postprandial hyperglycemia. Carbohydrate is the primary dietary macronutrient that causes postprandial hyperglycemia. Thus, we investigated whether carbohydrate intake was associated with the GA/HbA1c ratio in patients with type 2 diabetes. *Methods*: Daily energy intake and carbohydrate intake were estimated in twenty-two patients with type 2 diabetes who received no pharmacological therapy (18 men and 4 women, age 53 ± 11 years old). The energy index and the carbohydrate index were defined as the ratio of daily energy intake to body weight and daily carbohydrate intake to body weight, respectively. *Results*: The energy index was significantly correlated with the GA/HbA1c ratio ($r = 0.451$, $p = 0.035$), but not with fasting plasma glucose (FPG), HbA1c and GA. The carbohydrate index was significantly correlated with GA ($r = 0.461$, $p = 0.031$) and the GA/HbA1c ratio ($r = 0.554$, $p = 0.007$), but not with FPG and HbA1c. Multivariate analysis revealed that the carbohydrate index was independently associated with the GA/HbA1c ratio ($\beta = 0.397$, $p = 0.046$). *Conclusions*: The carbohydrate index was significantly correlated with GA and the GA/HbA1c ratio in the patients with type 2 diabetes. These results suggest that carbohydrate intake may be associated with the GA/HbA1c ratio through postprandial hyperglycemia.**

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Keywords

Glycated Albumin, HbA1c, Type 2 Diabetes Mellitus, Carbohydrate, Postprandial Hyperglycemia

1. Introduction

The primary dietary macronutrient that causes postprandial hyperglycemia and hyperinsulinemia is carbohydrate [1]. This observation led to the dietary intervention with low carbohydrate diets for patients with diabetes [2]. Similarly, carbohydrate counting is the approach to adjust pre-meal insulin dosages based on the amount of carbohydrate in the meal. In addition, carbohydrate-restricted diet causes the attenuation of postprandial hyperglycemia and the decrease of the incremental insulin secretion after meal [3].

HbA1c, which is used as a gold standard of glycemic control, reflects mainly mean plasma glucose during the last 2 to 3 months. In contrast, glycated albumin (GA), another glycemic control marker for the shorter period (about 2 weeks), is known to reflect postprandial hyperglycemia as well as mean plasma glucose [4]. It has been shown that patients with type 1 diabetes have significantly higher GA/HbA1c ratios than patients with type 2 diabetes [5]. Generally, patients with type 1 diabetes are prone to have higher postprandial hyperglycemia and larger glycemic excursion. Taken together with these results, GA reflects postprandial hyperglycemia and glycemic excursion better than HbA1c. Moreover, the investigations using continuous glucose monitoring (CGM) systems demonstrated that both GA and the GA/HbA1c ratio, but not HbA1c, were correlated with various indices of glycemic excursions [6] [7]. We also demonstrated that the administration of metformin [8] or sitagliptin, dipeptidylpeptidase-4 [DPP4] inhibitor [9], decreased the GA/HbA1c ratio due to their improvements of postprandial hyperglycemia.

Based on the fact that carbohydrate intake is correlated with postprandial hyperglycemia in patients with type 2 diabetes who receive no pharmacological therapy, it is possible that carbohydrate intake may be correlated with the GA/HbA1c ratio in such patients. To examine this possibility, we investigated the associations between total energy intake and carbohydrate intake with various indices of glycemiain patients with type 2 diabetes who receive no pharmacological therapy.

2. Materials and Methods

2.1. Study Patients

Twenty-two pharmacological therapy-naïve patients with type 2 diabetes attending Nissay Hospital between January 2011 and December 2011 [18 men and 4 women, aged 53 ± 11 years old, body mass index (BMI) 26.2 ± 5.0 kg/m^2] (**Table 1**) were included. Diabetes mellitus was diagnosed according to American Diabetes Association criteria. Patients with symptoms of hyperglycemia, chronic liver disease, chronic kidney disease and thyroid disease were excluded. The study was conducted in accordance with the Declaration of Helsinki and the approval of the Ethics Committee of Nissay Hospital. Each patient provided written informed consent for the study participation and the use of their data for research purposes.

2.2. Laboratory Methods

A registered dietitian calculated daily total energy intake and carbohydrate intake based on dietary questionnaires for three consecutive days. The energy index and the carbohydrate index were defined as the value of daily energy intake divided by body weight and daily carbohydrate intake divided by body weight, respectively. Plasma glucose was determined using the hexokinase, glucose-6-phosphate dehydrogenase method. HbA1c levels were measured with HLC-723G8 (Tosoh, Tokyo, Japan) by high performance liquid chromatography (HPLC). The value for HbA1c (%) was shown as a National Glycohemoglobin Standardization Program (NGSP) value [10]. GA was determined with a Hitachi 7600 autoanalyzer (Hitachi Instruments Service Co., Tokyo, Japan) by an enzymatic method using albumin-specific proteinase, ketoamine oxidase and albumin assay reagent (Lucica GA-L; Asahi Kasei Pharma Co., Tokyo, Japan) [11].

2.3. Statistical Analyses

All data are shown as means ± SD. For statistical analyses, the paired Student's *t* test was used to compare the

two groups. Univariate regression analysis as well as stepwise multivariate regression analysis was performed with the Stat View computer program (Version 5.0 for Windows, Abacus Concepts, Berkeley, CA). In the stepwise multiple regression analysis, the F-value for the inclusion of the variables was set at 4.0. P value of <0.05 was considered statistically significant.

3. Results

Fasting plasma glucose (FPG), HbA1c, GA, and the GA/HbA1c ratio of the study patients were 174 ± 50 mg/dL, 8.9% ± 1.9%, 24.4% ± 7.6%, and 2.70 ± 0.37, respectively (**Table 1**). The energy intake and the carbohydrate intake were 2060 ± 445 kcal/day and 1030 ± 321 kcal/day, respectively. The ratio of carbohydrate intake in total energy intake was 52% ± 18%. The energy index and the carbohydrate index were 28.6 ± 5.8 kcal/kg/day and 14.4 ± 4.5 kcal/kg/day, respectively.

Neither the energy intake nor the carbohydrate intake was significantly correlated with FPG, HbA1c, GA and the GA/HbA1cratio (**Table 2**). The carbohydrate intake/energy intake ratio was also not significantly correlated with FPG, HbA1c, GA and the GA/HbA1c ratio. The energy index was significantly correlated with the GA/HbA1cratio ($r = 0.451$, $p = 0.035$), but not with FPG, HbA1c and GA. The carbohydrate index was significantly correlated with GA ($r = 0.461$, $p = 0.031$) and the GA/HbA1c ratio ($r = 0.554$, $p = 0.007$), but not with FPG and HbA1c.

Stepwise multivariate analysis with the GA/HbA1c ratio as the dependent variable and sex, age, BMI, energy index and carbohydrate index as the independent variables revealed that only the carbohydrate index was selected as the significant variable ($\beta = 0.397$, $p = 0.046$) (**Table 3**). Interestingly, although BMI was inversely correlated with the GA/HbA1c ratio in univariate analysis ($r = -0.548$, $p = 0.008$), BMI was no longer correlated with the GA/HbA1c ratio in multivariate analysis.

4. Discussion

To our knowledge, this is the first report that the carbohydrate index (carbohydrate intake per body weight) was

Table 1. Clinical characteristics of study patients.

n	22
Men (%)	18 (81.8)
Age (years)	53 ± 11
Body mass index (kg/m^2)	26.2 ± 5.0
Fasting plasma glucose (mg/dL)	174 ± 50
HbA1c (%)	8.9 ± 1.9
GA (%)	24.4 ± 7.6
GA/HbA1c ratio	2.70 ± 0.38
Energy intake (kcal/day)	2060 ± 445
Energy index (kcal/kg/day)	28.6 ± 5.8
Carbohydrate intake (kcal/day)	1030 ± 321
Carbohydrate index (kcal/kg/day)	14.4 ± 4.5
Carbohydrate intake/energy intake (%)	52 ± 18

Table 2. Correlation between energy intake, energy index, carbohydrate intake, carbohydrate index or carbohydrate intake/energy intake and various glycemic control markers.

	Energy intake		Energy index		Carbohydrate intake		Carbohydrate index		Carbohydrate intake/energy intake	
	R	P	R	P	R	P	R	P	R	P
FPG	0.166	0.488	0.229	0.304	0.285	0.199	0.301	0.173	0.188	0.403
HbA1c	0.100	0.657	0.168	0.455	0.304	0.169	0.344	0.117	0.255	0.252
GA	0.019	0.934	0.299	0.177	0.291	0.188	0.461	0.031	0.283	0.202
GA/HbA1c	0.064	0.813	0.451	0.035	0.255	0.251	0.554	0.007	0.276	0.214

Table 3. Stepwise multivariate regression analyses on the GA/HbA1c ratio in 22 untreated patients with type 2 diabetes mellitus.

Variable	β	F	P
Carbohydrate index	0.397	4.37	0.046
BMI	–0.385	4.12	0.274

Dependent variables included are gender (female: 0, male: 1), age (years), BMI (kg/m^2), energy index (kcal/kg/day) and carbohydrate index (kcal/kg/day). $R^2 = 0.373$, $F = 7.73$, and $p = 0.016$.

correlated with the GA/HbA1c ratio in drug-naive patients with type 2 diabetes.

Because GA reflects shorter-term glycemic control compared to HbA1c, the GA/HbA1c ratio shows low levels when plasma glucose recently decreases, and it shows high levels when plasma glucose recently increases [12] [13]. In addition, we report that the GA/HbA1c ratio in patients with fulminant type 1 diabetes, in which a marked hyperglycemia develops in a very short-term after the onset, is significantly greater than that in patients with type 2 diabetes [14]. Patients with symptoms of hyperglycemia were excluded in the present study because they may have elevated GA/HbA1c ratio due to recent aggravation of glycemic controls. Therefore, the study patients were all asymptomatic and diagnosed as diabetes in health-checkup or in laboratory examination for other diseases. Because the GA/HbA1c ratio in the study patients (2.70 ± 0.37) is not significantly different from that of patients with type 2 diabetes whose glycemic control is stable (2.69 ± 0.33) [15], the glycemic control of our patients is suggested to be stable.

The effect of dietary carbohydrate is often determined by the carbohydrate intake (g/day) or the carbohydrate intake/energy intake ratio. In the present study, the carbohydrate index (g/kg/day), but not the carbohydrate intake and the carbohydrate intake/energy intake ratio is significantly correlated with the GA/HbA1c ratio. These results suggest that the carbohydrate index, rather than the carbohydrate intake or the carbohydrate intake/ energy intake ratio, might reflect postprandial hyperglycemia. In order to confirm our findings, it is necessary to study with a large number of patients in the future.

Some of the oral hypoglycemic agents improve postprandial hyperglycemia. In this regard, we reported that met form in [8] and sitagliptin, DPP4 inhibitor [9], decreased the GA/HbA1c ratio. To avoid the effect of hypoglycemic agents on the GA/HbA1c ratio, we excluded patients taking hypoglycemic agents from the present study.

Previous reports showed that postprandial hyperglycemia was associated with cardiovascular diseases and mortality [16] [17]. In addition, there are reports indicating the association of postprandial hyperglycemia with other disease conditions. Ohara *et al*. reported that cognitive impairment was associated with 2-hour post load glucose levels but not with FPG and HbA1c [18]. Shiraiwa *et al.* demonstrated that postprandial hyperglycemia was associated with the development and progression of diabetic retinopathy [19].

GA and the GA/HbA1c ratio are shown to be inversely correlated with BMI [20]-[22]. In the present study, we found that BMI was inversely correlated with the GA/HbA1c ratio in univariate analysis, but that was not the case in multivariate analysis. In the multivariate analysis, only the carbohydrate index was independently associated with the GA/HbA1c ratio. These results suggest that carbohydrate index but not BMI has a greater effect on the GA/HbA1c ratio in patients with untreated type 2 diabetes.

The present study has several limitations. First, our study was performed in a relatively small number of patients. Further studies with a greater number of patients are necessary. Second, we failed to measure postprandial plasma glucose levels. Measurement of postprandial glucose by self-monitoring of blood glucose or CGM is necessary in the future study. Third, we were unable to infer the causative relationship between carbohydrate index and the GA/HbA1c ratio due to cross-sectional design of our study. The relationship should be determined with prospective cohort study. Finally, we only determined the amount of carbohydrate but not the quality of carbohydrate as to glycemic index. Because previous studies reported that carbohydrate with low glycemic index attenuated glycemic excursions and increased incremental insulin after meals [23] [24], both the amount and quality of dietary carbohydrate should be determined in the future study.

In conclusion, the carbohydrate index (carbohydrate intake per body weight) is correlated with the GA/HbA1c ratio, a marker reflecting postprandial hyperglycemia, in patients with untreated type 2 diabetes. A prospective cohort study with a greater number of patients is warranted to investigate the relationship between the carbohy-

drate index and postprandial hyperglycemia.

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None of the authors have conflicts of interest to declare.

Competing Interests

All authors had no conflicts of interest.

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Ethical Approval

The ethics committee of Nissay Hospital approved this study and written informed consent was obtained from each subject.

Contributions

S. S. researched literature, conceived the study, researched data, contributed to the discussions, wrote and edited the manuscript. Y. U., S. N., K. O., A. K., S. I., A. D., B. S., I. T. researched data, contributed to the discussion and edited the manuscript. S. K. contributed to the discussion, and reviewed and edited the manuscript. M. K. wrote and edited the manuscript and contributed to the discussion. All authors approved its final version.

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