Correlation of glycated albumin but not hemoglobin A1c with endogenous insulin secretion in fulminant type 1 diabetes mellitus

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ABSTRACT

Aims/Introduction: Fulminant type 1 diabetes mellitus (FT1DM) develops as a result of very rapid and almost complete pancreatic β-cell destruction. We hypothesized that in patients with FT1DM who have less endogenous insulin secretion, disease progression is more rapid, and thus glycated albumin (GA) levels are lower. This study was designed to prove this hypothesis.

Materials and Methods: The present study included 42 patients with FT1DM (24 men, 18 women) in whom glycated hemoglobin (HbA1c), GA and daily urinary C-peptide (CPR) were measured at the time of diagnosis. Patients with complications, such as liver disease, kidney disease, anemia, or who were pregnant were excluded.

Results: Urinary CPR (log transformed) was not correlated with HbA1c (\( R = 0.168, P = 0.287 \)), but was positively correlated with GA (\( R = 0.336, P = 0.030 \)). It was weakly, but not significantly, correlated with GA/HbA1c ratio (\( R = 0.281, P = 0.072 \)). In patients with GA < 24.0%, urinary CPR was significantly lower than in patients with GA ≥ 24.0%. In addition, in patients with GA/HbA1c ratio <3.8, urinary CPR was significantly lower than in patients with GA/HbA1c ratio ≥ 3.8.

Conclusions: Our findings suggest that in patients with FT1DM, GA at the time of diagnosis was correlated with endogenous insulin secretion. GA < 24.0% at the time of diagnosis is predictive for less endogenous insulin secretion in patients with FT1DM.

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KEY WORDS: Glycated albumin, Fulminant type 1 diabetes mellitus, C-peptide

INTRODUCTION

Fulminant type 1 diabetes mellitus (FT1DM) is a novel subtype of type 1 diabetes (T1DM) reported in 2000 by Imagawa et al. FT1DM develops as a result of very rapid and almost complete pancreatic β-cell destruction1,2. FT1DM has been shown to account for approximately 20% of Japanese patients with T1DM3. At the time of onset of FT1DM, plasma glucose (PG) is markedly elevated, in contrast to glycated hemoglobin (HbA1c), which out of proportion to PG, is normal or only slightly elevated. Therefore, the recommended diagnostic criteria for FT1DM include a very rapid onset of diabetic ketoacidosis (DKA) together with low serum or urinary C-peptide (CPR; which reflects decreased endogenous insulin secretion), marked hyperglycemia and a relatively low HbA1c to PG ratio4,5.

In diabetes, as compared with non-diabetes, glycation of several proteins is known to be increased, thus suggesting that some play a role in the onset and progression of chronic diabetes complications6. Among these glycated proteins, HbA1c is widely used clinically as an index of glycemic control7. Meanwhile, glycated albumin (GA) has also become accepted as another index of glycemic control8. Thus, GA reflects more acute glycemic changes9. FT1DM is characterized by acutely elevated PG, so we have shown that whereas HbA1c is only slightly elevated, GA is relatively elevated, reflecting acutely elevated PG10.

Individual differences are seen in the degree of residual endogenous insulin secretion among FT1DM patients. We hypothesized that in patients with FT1DM who have less endogenous insulin secretion, disease progression is more rapid, and thus levels of HbA1c and GA are lower. The present study was designed to prove this.
MATERIALS AND METHODS

Patients
Among FT1DM patients identified by a survey research committee or already reported, we enrolled 42 patients in whom HbA1c, GA and daily urinary CPR were measured when FT1DM was diagnosed (24 men, 18 women; mean age 43.1 ± 15.3 years; Table 1). FT1DM was diagnosed based on criteria by a Japanese T1DM Survey Research Committee3-4. In some patients with a urinary CPR exceeding 10 μg/day, the diagnosis of FT1DM was based on serum CPR levels (fasting serum CPR < 0.3 ng/mL, or serum CPR < 0.5 ng/mL after glucagon injection or meal load soon after disease onset). Because of possible effects on measured values of HbA1c and GA, patients with complications, such as anemia, liver disease, kidney disease, or who were pregnant were excluded from the present study.

Laboratory Methods
Plasma glucose was determined using the glucose-oxidase method. HbA1c was measured by high performance liquid chromatography (HPLC), with calibration using Japan Diabetes Society (JDS) Lot 212. Serum GA was determined by enzymatic methods using albumin-specific protease, ketoamine oxidase and an albumin assay reagent (Lucica GA-L; Asahi Kasei Pharma, Tokyo, Japan)13,14. Glycated albumin was hydrolyzed to amino acids by an albumin-specific proteinase, and then oxidized by ketoamine oxidase to produce hydrogen peroxide, which was measured quantitatively. Glycated albumin level was calculated as the percentage of GA relative to total albumin, which was measured in the same serum sample using a new bromocresol purple method13.

Statistical Analysis
All data are shown as means ± SD. To correct for skewed distributions, urinary CPR excretion concentrations were logarithmically transformed. In statistical analyses, urinary CPR was assigned at 0.1 μg/day when it was undetectable levels (13 patients). For statistical analysis, the Mann–Whitney U-test was used to compare the two groups. To analyze the effects of explanatory variables on urinary CPR, univariate regression analysis was carried out using StatView software (Version 5.0 for Windows, Abacus Concepts, Berkeley, CA, USA). A P-value of <0.05 was considered to be statistically significant.

RESULTS
Urinary CPR (log transformed) was not correlated with HbA1c (R = 0.168, P = 0.287), but was positively correlated with GA (R = 0.336, P = 0.030) in the study patients (Figure 1). Urinary CPR was weakly, but not significantly, correlated with GA/HbA1c ratio (R = 0.281, P = 0.072). In patients with HbA1c < 6.2% (n = 24), compared with those with HbA1c ≥ 6.2% (n = 18), urinary CPR did not significantly differ (2.9 ± 3.2 vs 3.9 ± 3.7 μg/day; P = 0.322; Figure 2). By contrast, in patients with GA < 24.0% (n = 24), compared with those with GA ≥ 24.0% (n = 18), urinary CPR was significantly lower (2.3 ± 2.9 vs 4.7 ± 3.7 μg/day; P = 0.027). In addition, in patients with GA/HbA1c ratio < 3.8 (n = 12), compared with those with GA/HbA1c ratio ≥ 3.8 (n = 30), urinary CPR was significantly lower (1.4 ± 2.4 vs 4.1 ± 3.5 μg/day; P = 0.022; Figure 2).

Fasting serum CPR was not associated with HbA1c (R = 0.253, P = 0.155) and GA (R = 0.247, P = 0.166) in 33 patients. Serum CPR after the glucagon injection was not associated with HbA1c (R = 0.415, P = 0.077) and GA (R = 0.397, P = 0.092) in 19 patients who had glucagon stimulation test.

DISCUSSION
The present study found no correlation between urinary CPR and HbA1c in FT1DM patients, but urinary CPR was significantly correlated with GA and GA/HbA1c ratio. In FT1DM, because of acute destruction of pancreatic β-cells, insulin secretion is depleted, and DKA rapidly develops. The diagnostic criteria for FT1DM include a low (<10 μg/day) urinary CPR, known index of endogenous insulin secretion13,14, and indeed, most study patients had values < 10 μg/day. However, among the patients, the values were distributed over a range from undetectable or very low up to 14 μg/day. We were able to postulate that in patients with undetectable urinary CPR, DKA rapidly develops, whereas in patients with even minimal residual pancreatic β-cell function, the time to onset of DKA is longer.

In contrast to urinary CPR, serum CPR before and after the glucagon stimulation test showed no significant association with HbA1c and GA. These results suggest that urinary CPR rather than serum CPR might more accurately reflect endogenous insulin secretion in FT1DM patients.

It is suggested that GA, which more so than HbA1c, reflects acute PG changes, is higher in FT1DM patients in whom time to development of DKA is longer after the onset of hyperglycemic symptoms. In contrast, because HbA1c is only slightly elevated with acute rises in PG, HbA1c values do not reflect well the time to development of DKA. Because GA, compared with...
HbA1c markedly increases with acute rises in PG, as seen in FT1DM, the GA/HbA1c ratio is high before treatment of FT1DM1. Meanwhile, when PG acutely decreases, GA markedly decreases, whereas HbA1c only slightly decreases, so the GA/HbA1c ratio is lower9. In the present study, GA was well correlated with urinary CPR in FT1DM patients, suggesting the usefulness of GA as indexes of short-term glycemic changes. On the contrary, HbA1c has been shown to be inadequate to reflect short-term changes in PG in FT1DM patients.

We found significant correlations of GA with urinary CPR. In addition, cut-off values of GA of 24.0% and GA/HbA1c ratio of 3.8 were found to discriminate between urinary CPR levels in the study patients. These data suggest that GA and the GA/HbA1c ratio are set relatively higher with longer disease duration until development of DKA after symptom onset in patients who had relatively higher endogenous insulin secretion. However, we failed to show the correlation of estimated disease duration with GA and urinary CPR (data not shown).
Conversely, the estimated disease duration based on the medical history might be unreliable. FT1DM patients sometimes do not present with typical symptoms, such as thirst, polydipsia and polyuria; they can also present with non-specific symptoms, such as fatigue\textsuperscript{15}. Therefore, estimated disease duration diagnosed by physicians might be inaccurate. By referring GA, actual disease duration in FT1DM might be able to be calculated. In the future, the relationship of the disease duration with GA and urinary CPR should be evaluated in FT1DM patients.

In conclusion, our findings suggest that GA at the diagnosis of FT1DM was correlated with patients’ endogenous insulin secretion. GA < 24.0% or GA/HbA1c ratio < 3.8 at the time of diagnosis is predictive for less endogenous insulin secretion, and thus might indicate difficulties in obtaining good glycemic control. More intensive diabetes management would be necessary in FT1DM patients with GA < 24.0% or GA/HbA1c ratio < 3.8 at the time of diagnosis.

\section*{ACKNOWLEDGEMENT}
None of the authors have conflicts of interest to declare.

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