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□ ORIGINAL ARTICLE □

Major Increases between Pre- and Post-breakfast Glucose Levels May Predict Nocturnal Hypoglycemia in Type 2 Diabetes

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Abstract

Objective The aim of this study was to determine whether nocturnal hypoglycemia may be predicted according to morning glucose levels.

Methods We retrospectively evaluated 106 patients with type 2 diabetes who underwent continuous glucose monitoring during admission. The pre-breakfast glucose level (Pre-breakfast level), highest postprandial glucose level within 3 hours after breakfast (Highest level), time from the start of breakfast to the highest postprandial glucose level (Highest time), difference between the pre-breakfast and highest postprandial breakfast glucose levels (Increase), area under the glucose curve (≥180 mg/dL) within 3 hours after breakfast (Morning AUC), post-breakfast glucose gradient (Gradient), and the increase-to-pre-breakfast ratio (Increase/Pre-breakfast) were calculated. The subjects were divided into hypoglycemic and non-hypoglycemic patients and compared for the above parameters using the *t*-test. A receiver operating characteristic analysis was used to determine the optimal cut-off values to predict nocturnal hypoglycemia (Hypoglycemia).

Results Twenty-eight patients (26.4%) had hypoglycemia. The Pre-breakfast levels were significantly lower in patients with hypoglycemia than those without (p=0.03). The Increases were significantly higher in patients with hypoglycemia than those without (p=0.047). The Increase/Pre-breakfast ratio were significantly larger in patients with hypoglycemia than those without (p=0.0002). Their cut-off values were as follows (level, sensitivity, specificity, and area under the curve): 123 mg/dL, 0.89, 0.55, and 0.78 (p<0.0001); 90.5 mg/dL, 0.75, 0.64, and 0.76 (p<0.0001); and 90.2%, 0.75, 0.76, and 0.78 (p<0.0001), respectively.

Conclusion Major increases between the pre- and post-breakfast glucose levels may predict nocturnal hypoglycemia in patients with type 2 diabetes.

Key words: nocturnal hypoglycemia, morning glucose increases, type 2 diabetes

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Introduction

Large clinical studies have shown that hypoglycemia is strongly associated with mortality in patients with diabetes mellitus (1-4). Although a relationship between nocturnal hypoglycemia and sudden death has been suggested (5), predicting nocturnal hypoglycemia is challenging in patients with type 2 diabetes, as many of these patients are unaware of their conditions, especially patients with advanced disease or elderly patients (6).

Nocturnal hypoglycemia has been suggested to be associated with not only major hyperglycemia in daytime (7, 8), but also increased morning glucose levels (9). Thus, clinical significance is high if morning glycemic variability can predict the presence of nocturnal hypoglycemia. However, the

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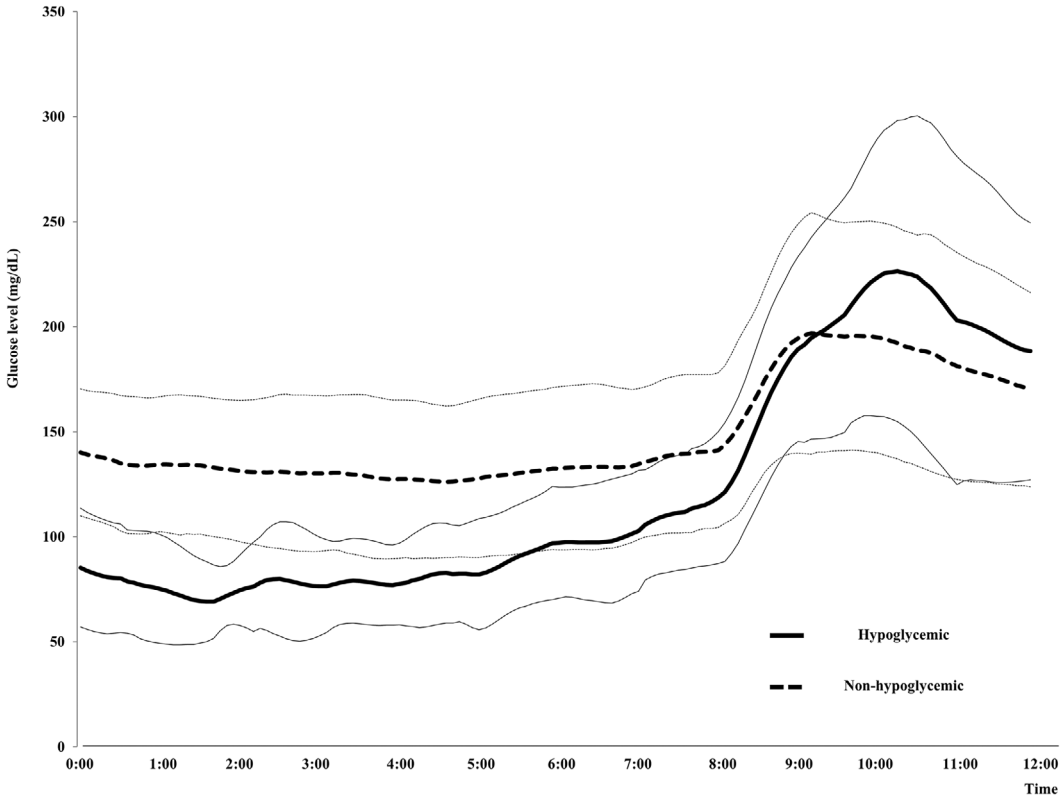

Figure 1. **The graph indicates glycemic variability from nighttime to morning of continuous glucose monitoring in hypoglycemic patients (p=28) or non-hypoglycemic patients (p=78). Data are shown as the mean (thick lines) and standard deviation (fine lines).**

mechanism of this relationship remains unknown. The Somogyi phenomenon (10, 11) is a cause of increased morning glucose levels. However, the dawn phenomenon (11, 12) can also cause increased morning glucose levels. Thus, an investigation based on continuous glucose monitoring from nighttime to morning is necessary to determine whether nocturnal hypoglycemia may be predicted based on morning glucose levels.

We therefore retrospectively studied whether nocturnal hypoglycemia may be predicted based on morning glucose levels in patients with type 2 diabetes using continuous glucose monitoring (13) (CGM) data.

Materials and Methods

Study design and patient selection

We retrospectively analyzed 106 patients with type 2 diabetes who underwent CGM during admission during a 2-year period from 2013 to 2015. The study was approved by the institutional review board of Ichinomiyanishi Hospital, Japan. All of the patient data extracted were anonymized.

Patients who were aware of their hypoglycemia and took glucose tablets and those who had been taking α-glucosidase inhibitors were excluded. We used CGM data measured with the Medtronic ipro2 device (Medtronic MiniMed, Northridge, USA). Nocturnal hypoglycemia was defined as a blood glucose level of <70 mg/dL occurring from 0 am to 8 am. The subjects were also evaluated for the duration of nocturnal hypoglycemia.

Outcomes and statistical analysis

The parameters used as indices of glycemic variability included pre-breakfast glucose level (Pre-breakfast level), highest postprandial glucose level within 3 hours after breakfast (Highest level), time from the start of breakfast to the highest postprandial glucose level (Highest time), difference between pre-breakfast and highest postprandial breakfast glucose levels (Increase), area under the glucose curve (≥180 mg/dL) within 3 hours after breakfast (Morning AUC), post-breakfast glucose gradient (Gradient), and the increased glucose level/pre-breakfast glucose level ratio (Increase/Pre-breakfast) (14).

The subjects were divided into hypoglycemic and non-hypoglycemic patients and compared for the above parameters using the *t*-test to examine whether the occurrence of nocturnal hypoglycemia may be predicted according to an analysis of these parameters. We analyzed the association between the patient characteristics [age, sex, duration of diabetes, body mass index (BMI), glycosylated hemoglobin (HbA1c) concentration, C-peptide index (CPI) and the presence of antidiabetic agents] and nocturnal hypoglycemia using a logistic regression analysis. A receiver operating characteristic (ROC) analysis was used to determine the optimal

Table 1. Sample Characteristics and Parameters for Glycemic Variability Compared between Hypoglycemic and Non-hypoglycemic Patients.

Characteristic	Overall	Hypoglycemic	Non-hypoglycemic	p
N (Male / Female)	106 (56 / 50)	28 (11 / 17)	78 (45 / 33)	p_2=0.09
Age, years	66.6 ± 11.0	69.8 ± 10.1	65.5 ± 11.2	p_1=0.07
Duration of diabetes, years	14.7 ± 10.7	15.9 ± 11.4	14.3 ± 10.5	p_1=0.51
BMI, kg/m^2	23.7 ± 3.9	22.7 ± 2.9	24.1 ± 4.2	p_1=0.07
HbA1c (NGSP), %	8.7 ± 1.4	8.9 ± 1.7	8.6 ± 1.3	p_1=0.34
HbA1c (IFCC), mmol/mol	71.2 ± 15.6	73.9 ± 18.3	70.2 ± 14.6	p_1=0.34
CPI	1.0 ± 0.8	1.0 ± 1.0	1.0 ± 0.7	p_1=0.87
Total daily insulin dose, U	21.1 ± 16.3	22.5 ± 20.6	20.4 ± 14.0	p_1=0.65
Basal insulin ratio, %	75.7 ± 26.5	79.3 ± 25.2	74.0 ± 27.1	p_1=0.42
Nighttime duration of hypoglycemia, min	51.7 ± 89.7	161.2 ± 86.2	0 ± 0	p_1<0.0001
Pre-breakfast glucose level, mg/dL	128.7 ± 33.8	115.8 ± 35.4	133.4 ± 39.1	p_1=0.03
Highest glucose level, mg/dL	226.4 ± 62.7	252.1 ± 75.6	217.2 ± 55.6	p_1=0.03
Highest glucose time, min	100.8 ± 42.2	114.4 ± 41.0	96.0 ± 41.7	p_1=0.047
Increase glucose level, mg/dL	97.7 ± 56.3	136.3 ± 56.8	83.9 ± 49.6	p_1<0.0001
AUC (≥180 mg/dL), mg・min/dL	7,027.4 ± 9,268.6	11,254.4 ± 12,831.5	5,510.0 ± 7,112.1	p_1=0.03
Glucose gradient, mg/dL・min	1.1 ± 1.2	1.3 ± 0.5	1.1 ± 1.4	p_1=0.35
Increase/Pre-breakfast, %	85.4 ± 62.5	124.7 ± 66.0	71.3 ± 57.4	p_1=0.0002
Sulfonylurea agent, n (%)	10 (9.4)	2 (7.1)	8 (10.3)	p_2=0.63
Metformin, n (%)	68 (64.2)	16 (57.1)	52 (66.7)	p_2=0.37
Thiazolidinediones, n (%)	17 (16.0)	7 (25.0)	10 (12.8)	p_2=0.13
α- glucosidase inhibitor, n (%)	0 (0)			
Insulin, n (%)	70 (66.0)	20 (71.4)	50 (66.0)	p_2=0.48
DPP-4 inhibitors, n (%)	58 (54.7)	19 (67.9)	39 (50.0)	p_2=0.1
GLP-1 receptor agonists, n (%)	13 (12.3)	5 (17.9)	8 (10.3)	p_2=0.29
Rapid-acting insulin secretagogue, n (%)	11 (10.4)	3 (10.7)	8 (10.3)	p_2=0.95
SGLT 2 inhibitor, n (%)	19 (17.9)	3 (10.7)	16 (20.5)	p_2=0.25
Insulin or sulfonylurea agent/Other agents	76/30	22/6	54/24	p_2=0.35

Data are shown as the mean and standard deviation (SD). p_1: Welch's *t*-test, p_2: Chi-square test. BMI: body mass index, HbA1c: glycosylated hemoglobin, CPI: C-peptide index, Highest glucose level, highest postprandial glucose level within 3 h after breakfast; Highest glucose time, time from the start of breakfast to the highest postprandial glucose level; Increase glucose level, difference between pre-breakfast and highest postprandial breakfast glucose levels; AUC (≥180 mg/dL), area under the glucose curve (≥180 mg/dL) within 3 h after breakfast; Glucose gradient, post-breakfast glucose gradient; Increase/Pre-breakfast, the increased glucose level/pre-breakfast glucose level ratio; Hypoglycemia, nocturnal hypoglycemia (<70 mg/dL occurring from 0 am to 8 am); DPP: dipeptidyl-peptidase, GLP: glucagon-like peptide, SGLT: sodium glucose co-transporter

cut-off values to predict nocturnal hypoglycemia (Hypoglycemia) (15). A p value <0.05 was considered to be statistically significant. Data are shown as the mean and standard deviation (SD).

Results

Patient characteristics

Fig. 1 shows glycemic variability from nighttime to morning of CGM in hypoglycemic patients (n=28) and non-hypoglycemic patients (n=78). Table 1 shows sample characteristics and parameters for glycemic variability compared between hypoglycemic and non-hypoglycemic patients. The study included 56 men and 50 women. The baseline characteristics included: mean age of 66.6±11.0 years, body mass index of 23.7±3.9 kg/m^2, HbA1c level of 8.7±1.4 % (71.2±15.6 mmol/mol), duration of diabetes of 14.7±10.7 years, and C-peptide index (= fasting C-peptide immunoreactivity/FPG ×100) (CPI) of 1.0±0.8. Seventy subjects received insulin therapy [basal-bolus insulin therapy (n=27) or basal insulin therapy (n=43)] with long-acting insulin [insulin glargine (n=37) or insulin degludec (n=33)]. Long-acting insulin was injected once at 8 am. The indices of glycemic variability were as follows: Pre-breakfast level, 128.7±33.8 mg/dL; Highest level, 226.4±62.7 mg/dL; Highest time, 100.8±42.2 minutes; Increase, 97.7±56.3 mg/dL; Morning AUC, 7,027.4±9,268.6 mg·min/dL; Gradient, 1.1±1.2 mg/dL ·min; and the Increase/Pre-breakfast ratio, 85.4±62.5%. Twenty-eight patients (26.4%) had hypoglycemia. Hypoglycemic patients were shown to have nocturnal hypoglycemia lasting 161.2±86.2 minutes.

Primary outcomes

The Pre-breakfast levels were significantly lower among patients with hypoglycemia at 115.8±35.4 mg/dL compared to 133.4±39.1 mg/dL among those without (p=0.03). The Highest levels were significantly higher among patients with hypoglycemia at 252.1±75.6 mg/dL compared to 217.2±55.6 mg/dL among those without (p=0.03). The Highest times were significantly longer among patients with hypoglycemia at 114.4±41.0 minutes compared to 96.0±41.7 minutes

Table 2. The Relationship between Sample Characteristics and Hypoglycemia.

(n = 106)	Hypoglycemia	
Variable	OR (95% CI)	p
Age, years	1.04 (0.995-1.09)	0.08
Male sex, n	0.47 (0.20-1.15)	0.1
Duration of diabetes, years	1.01 (0.97-1.06)	0.49
BMI, kg/m^2	0.91 (0.81-1.03)	0.13
HbA1c (NGSP), %	1.18 (0.87-1.59)	0.28
CPI	1.05 (0.61-1.81)	0.85
Total daily insulin dose, U	1.01 (0.98-1.04)	0.6
Basal insulin ratio, %	2.16 (0.33-14.16)	0.42
Sulfonylurea agent, n	0.67 (0.13-3.38)	0.63
Metformin, n	0.67 (0.28-1.61)	0.36
Thiazolidinediones, n	2.27 (0.77-6.69)	0.14
Insulin, n	1.40 (0.55-3.59)	0.48
DPP-4 inhibitors, n	2.11 (0.85-5.24)	0.11
GLP-1 receptor agonists, n	1.90 (0.57-6.40)	0.3
Rapid-acting insulin secretagogue, n	1.05 (0.26-4.27)	0.95
SGLT 2 inhibitor, n	0.47 (0.12-1.74)	0.25
Insulin or Sulfonylurea agent, n	1.63 (0.59-4.53)	0.35

Data were analyzed using a univariate logistic regression analysis.
OR: odds ratio, CI: confidence interval

among those without (p=0.047). The Increases were significantly higher among patients with hypoglycemia at 136.3±56.8 mg/dL compared to 83.9±49.6 mg/dL among those without (p=0.047). The Morning AUC were significantly larger among patients with hypoglycemia at 11,254.4±12,831.5 mg·min/dL compared to 5,510.0±7,112.1 mg·min/dL among those without (p=0.03). The Increase/Pre-breakfast ratio were significantly larger among patients with hypoglycemia at 124.7±66.0% compared to 71.3±57.4% among those without (p=0.0002). The Gradient was not significantly different between the two groups (Table 1).

According to a univariate analysis, the patient characteristics and use of antidiabetic agents were not associated with Hypoglycemia (Table 2).

In the subjects receiving insulin therapy, the total daily insulin dose and basal insulin ratio were not associated with Hypoglycemia. Insulin degludec (vs. insulin glargine) therapy was associated with Hypoglycemia (OR, 0.32; 95% CI, 0.11-0.92; p=0.03).

Fig. 2 shows the ROC curves for hypoglycemia according to the indices of glycemic variability. Regarding the Pre-breakfast glucose level, a cut-off value of 123 mg/dL, which had the highest predictive ability, had a sensitivity of 89% and specificity of 55%. The AUC for hypoglycemia was 0.78 (95% CI 0.68-0.87, p<0.0001). Regarding Increase, a cut-off value of 90.5 mg/dL, which had the highest predictive ability, had a sensitivity of 75% and specificity of 64%. The AUC for hypoglycemia was 0.76 (95% CI 0.65-0.86, p<0.0001). Regarding the Increase/Pre-breakfast ratio, a cut-off value of 90.2%, which had the highest predictive ability, had a sensitivity of 75% and specificity of 76%. The AUC for hypoglycemia was 0.78 (95% CI 0.69-0.87, p<0.0001).

Discussion

A high risk of abnormal QT prolongation in the early morning in diabetic and non-diabetic patients with severe hypoglycemia has been reported (16). The relationships between hypoglycemia and abnormal QT prolongation, cardiac arrhythmia, and sudden death in patients with type 2 diabetes have been also reported (17). High risks of silent hypoglycemia and arrhythmias in patients with type 2 diabetes and cardiovascular diseases have been clarified (18). Thus, hypoglycemia in patients with type 2 diabetes may cause sudden death due to fatal arrhythmia, therefore hypoglycemia awareness is crucial. However, determining nocturnal hypoglycemia unawareness is difficult and often becomes problematic in everyday clinical practice (6).

On the other hand, hypoglycemia has been known to cause subsequent increases in the glucose level (Somogyi phenomenon) (19). Thus, if we evaluate patients with increased morning glucose levels in detail, we may detect patients who have nocturnal hypoglycemia. However, the causes of increased morning glucose levels are the effect of the dawn phenomenon (20) and increased glucose level after the first meal (breakfast) (21), as well as the Somogyi phenomenon, which are difficult to distinguish by merely measuring morning hyperglycemia. In fact, a previous report could not show the relationship between severe morning hyperglycemia and nocturnal hypoglycemia (22). Thus, we focused on not only morning hyperglycemia, but also glycemic variability from nighttime to morning using CGM. CGM allows for the detection of continuous glycemic variations and is useful to evaluate variability (23, 24). As a result, we suggest that nocturnal hypoglycemia may be predicted when pre-breakfast glucose levels are <120 mg/dL, glucose levels increase to ≥90 mg/dL, and the Increase/Pre-breakfast ratios are ≥90%. This indicates that patients who have highly elevated morning glucose levels, despite rather low pre-breakfast glucose levels, are likely to have nocturnal hypoglycemia. The results of the ROC analysis in this study suggest that simple pre-breakfast glucose levels can predict nocturnal hypoglycemia to the same degree as increased glucose levels or Increase/Pre-breakfast ratios. Naturally, lower pre-breakfast glucose levels can greater predict nocturnal hypoglycemia. As a result, it is significant that the predictive abilities of increased glucose levels or Increased/Pre-breakfast ratios are similar to the pre-breakfast glucose levels.

Although these results were analyzed using the CGM data, only two points can predict nocturnal hypoglycemia (pre- and post-breakfast levels). Therefore, it is possible to substitute the self-measurement of blood glucose (SMBG) for CGM. Determining nocturnal hypoglycemia unawareness by a 2-point SMBG is easy and useful with a high clinical significance. We consider that the Somogyi phenomenon is likely in patients with major increases between pre- and post-breakfast glucose levels, despite low pre-breakfast glu-

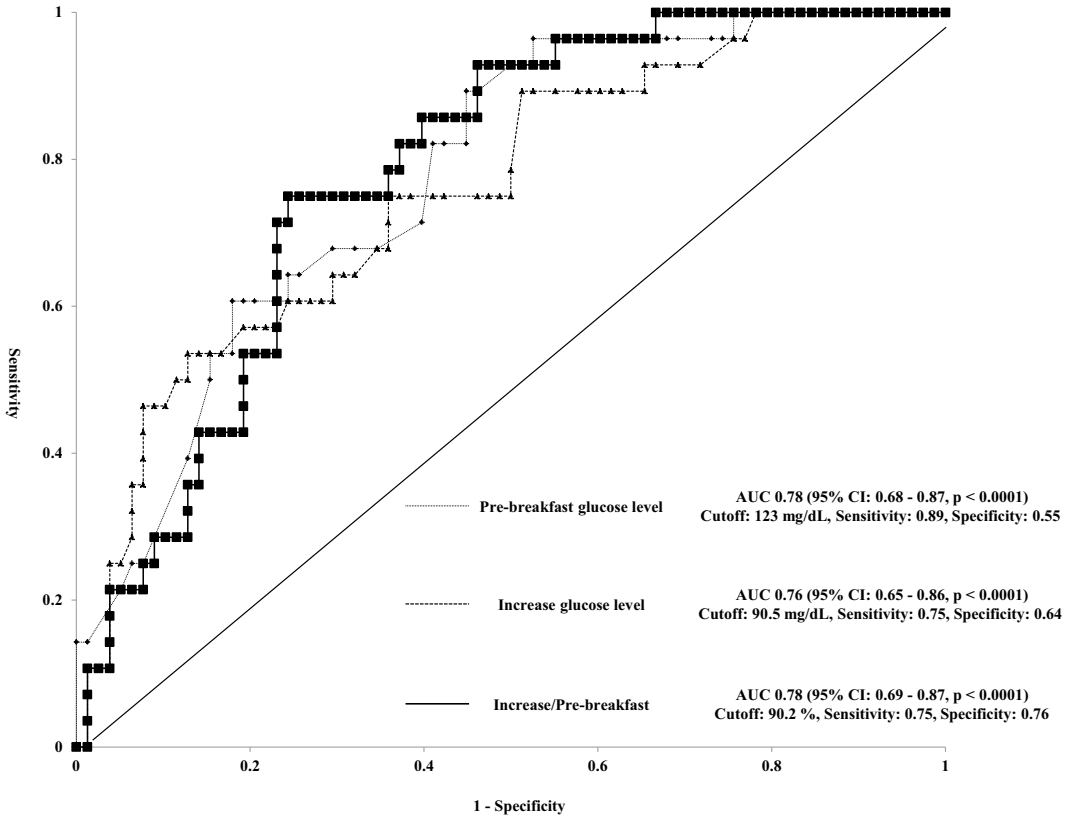

Figure 2. ROC curves for hypoglycemia in indices for glycemic variability. Pre-breakfast glucose level: The cut-off value of 123 mg/dL, which had the highest predictive ability, had a sensitivity of 89% and specificity of 55%. The AUC for hypoglycemia was 0.78 (95% CI 0.68-0.87, p<0.0001). Increase glucose level: The cut-off value of 90.5 mg/dL, which had the highest predictive ability, had a sensitivity of 75% and specificity of 64%. The AUC for hypoglycemia was 0.76 (95% CI 0.65-0.86, p<0.0001). Increase/Pre-breakfast: The cut-off value of 90.2%, which had the highest predictive ability, had a sensitivity of 75% and specificity of 76%. The AUC for hypoglycemia was 0.78 (95% CI 0.69-0.87, p<0.0001). ROC: receiver operating characteristic, AUC: area under the curve, CI: confidence interval, Increase glucose level, difference between pre-breakfast and highest postprandial breakfast glucose levels; Increase/Pre-breakfast, the increased glucose level/pre-breakfast glucose level ratio.

cose levels. In this case, we consider that treatments should be adjusted in order to reduce nocturnal hypoglycemia.

This study showed that major increases between pre- and post-breakfast glucose levels may predict nocturnal hypoglycemia in patients with type 2 diabetes. However, this study was conducted retrospectively and the antidiabetic agents used in this study were not standardized (sulfonylurea agent or insulin were used). Hence, the validity of these results must be evaluated in a prospective study where the use of antidiabetic agents is standardized.

The authors state that they have no Conflict of Interest (COI).

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