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Original Article

Effect of Glycemic Control on Chylomicron Metabolism and Correlation between Postprandial Metabolism of Plasma Glucose and Chylomicron in Patients with Type 2 Diabetes Treated with Basal-bolus Insulin Therapy with or without Vildagliptin

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***Aim*: Glucagon-like peptide-1 can reduce both postprandial plasma glucose (PG) and chylomicron (CM) levels in patients with type 2 diabetes. However, there have been no reports regarding the relationship between the postprandial metabolism of PG and CM.**

***Methods*: Patients with type 2 diabetes who were admitted for glycemic control were randomized to insulin alone (Ins; $n=16$) or insulin plus vildagliptin 100 mg (InsV; $n=16$) groups. The insulin dose was adjusted to maintain normal blood glucose levels. The daily profiles of serum TG, remnant lipoprotein cholesterol (RemL-C), and apolipoprotein B48 (ApoB48) were estimated by frequent blood collection on admission and before discharge, and the daily glucose fluctuation profile was also estimated using continuous glucose monitoring (CGM) before discharge.**

***Results*: The daily profiles of serum TG and RemL-C indicated a significant decrease before discharge compared with on admission; however, no significant changes in serum ApoB48 levels were observed in either group. At discharge, daily glucose fluctuation profile and the change in the serum ApoB48 level from fasting to the peak of the daily profile was significantly smaller in the InsV group than in the Ins group. The increment of serum ApoB48 level was significantly correlated with the mean amplitude of glycemic excursions calculated using CGM data only in the Ins group ($R^2=0.5242$, $P<0.001$).**

***Conclusions*: Short-term glycemic control decreased serum TG and RemL-C levels, but not ApoB48 levels, and the postprandial metabolism of PG and CM might be regulated by the same mechanism except GLP-1 effect.**

Key words: Apolipoprotein B48, Postprandial metabolism, Glucose fluctuation, Glycemic control, Dipeptidyl peptidase-4 inhibitor

Introduction

When treating diabetes mellitus, we aim to prevent the incidence and progression of complications that can be caused by continuous hyperglycemia. Many clinical trials have confirmed that continuous hyperglycemia causes microvascular and macrovascular complications[1-4]. Decreasing hemoglobin A_{1c} (HbA_{1c}) levels, a measure of mean plasma glucose (PG), can prevent microvascular complications[1, 2, 5], but macrovascular complications may be difficult to prevent[5-8]. In addition to mean blood glucose elevations, there has been strong evidence that postprandial hyperglycemia increases the incidence of coronary artery disease (CAD)[9, 10]. Administering an alpha glucosidase inhibitor can reduce postprandial blood glucose levels and prevent the incidence of CAD in patients with type 2 diabetes and in those with impaired glucose tolerance[11, 12].

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Apolipoprotein B48 (ApoB48) is the primary structural component of chylomicrons (CMs) and is a triglyceride (TG)-rich lipoprotein that is secreted by the intestine. Serum ApoB48 levels correlate with serum CM particle levels. Fasting hypertriglyceridemia is an independent risk factor for CAD in patients with type 2 diabetes[4], and we previously reported that fasting ApoB48 levels are independent risk factors for carotid artery plaque in patients with type 2 diabetes[13]. Moreover, ApoB48 can be detected in atherosclerotic plaque[14, 15], and elevated fasting ApoB48 levels are also considered to be a risk marker for CAD[16, 17]. Fasting serum ApoB48 levels are associated with postprandial serum TG and ApoB48 levels[18, 19]. Furthermore, postprandial hypertriglyceridemia in addition to fasting is an independent risk factor in the general population[20-22]. The overproduction of CMs was observed in an animal model of insulin resistance[23], and excess CM secretion has been associated with postprandial hypertriglyceridemia. Strict glycemic control with insulin therapy usually decreases serum TG levels; however, the effect of glycemic control on CM metabolism and the association between postprandial metabolism of PG and CM have not been reported.

Incretins, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are secreted by the intestinal tract following stimulation by nutrients and are immediately inactivated by dipeptidyl peptidase-4 (DPP-4). DPP-4 inhibitors (DPP-4Is), such as vildagliptin, inactivate DPP-4, thereby increasing active serum incretin levels in the postprandial state. Incretins, particularly GLP-1, enhance glucose-stimulated insulin secretion from pancreatic beta cells and attenuate glucagon secretion from pancreatic alpha cells. Incretins also decrease the rate of absorption of nutrients by decreasing gastric emptying and might directly decrease food intake by appetite suppression through central regulation[24]. A previous report showed that DPP-4Is and a short-acting GLP-1 receptor agonist ameliorate postprandial hyperglycemia in patients with type 2 diabetes[25, 26].

In the intestine, GLP-1 decreases the production of CMs in the postprandial state[27]. Previous reports have also suggested that GLP-1 receptor agonists and/or DPP-4Is can decrease postprandial serum TG and ApoB48 levels and ameliorate postprandial hyperglycemia in patients with type 2 diabetes[28-30].

We used frequent blood collection and a continuous glucose monitoring (CGM) system to assess the role of glycemic control in improving the daily profile of lipids and the correlation between the postprandial metabolism of PG and CM in patients with type 2 diabetes at the end of short-term hospitalization for glycemic control.

Materials and Methods

Subjects

Patients with type 2 diabetes, aged 20−75 years, who consulted the outpatient clinic of the Nippon Medical School Chiba Hokusoh Hospital from January 2012 to December 2013, who had HbA_{1c} levels of ≥10% at the first visit, and who agreed to hospitalization for diabetic control were eligible. Subjects were excluded if they were treated with insulin, DPP-4I, or GLP-1 receptor agonist or had a history or evidence of severe liver or renal disease, endocrine disease, recent myocardial infarction, cerebral vascular disease, heart failure, infectious disease, pregnancy, or any carcinoma.

Study Protocol and Treatment

On admission, all subjects discontinued taking any oral antidiabetic agents (OADs), underwent diet therapy, and were randomly assigned using a table of random sampling numbers to receive either insulin alone (Ins group) or insulin plus vildagliptin (InsV group).

Total calories of the daily diet (kcal/day) were calculated as 27.5 (kcal) × ideal body weight (IBW). IBW (kg) was calculated as $22 \times [\text{height (m)}]^2$, according to the evidence-based practice guideline for the treatment of diabetes of the Japan Diabetes Society. The daily diet comprised 25% fat and 20% protein. Each subject was provided with three meals per day at 8:00, 12:00, and 18:00.

To assess the daily profiles of serum TG, remnant lipoprotein cholesterol (RemL-C), ApoB48, C-peptide (CPR), and PG, blood specimens were obtained from the cubital vein 30 min before and 2 h after each meal (7:30, 10:00, 11:30, 14:00, 17:30, and 20:00), at night (23:00), and in the early morning (3:00) on the first day after admission and the last day before discharge. The blood samples collected between 7:30 and 14:00 were immediately centrifuged; those collected between 17:00 and 3:00 were stored at 4℃ and centrifuged the next morning.

To analyze PG, a portion of each blood sample was collected in a tube with NaF and anticoagulant and immediately centrifuged after collection. Serum and plasma were immediately collected after centrifugation and stored at −80℃ until assayed.

The daily profile of blood glucose was also assessed using a CGM system (iPro™2, Medtronic) for the last 2 days before discharge. To assess the daily glycemic variability, CGM data were used to calculate mean glucose, standard deviation (SD) of daily glucose, and mean amplitude of glycemic excursions (MAGE)[31]. The *M* value was also calculated from

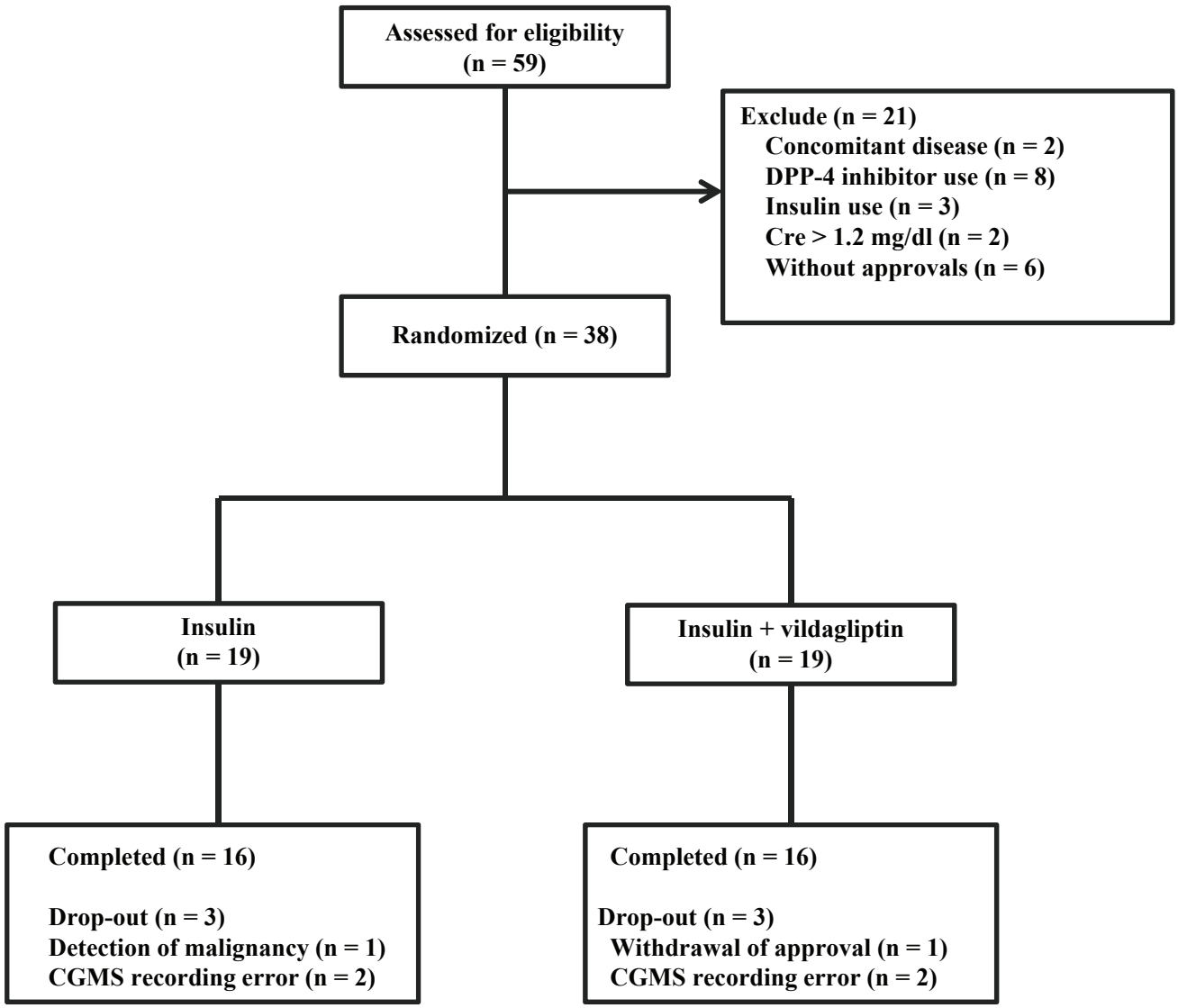

Fig. 1. Trial profile
Cre: creatinine

nine-point PG measurements[32].

The medication regimen was initiated after assessing the diurnal change of PG and serum lipids. The Ins group received basal-bolus insulin therapy (BBT) with insulin aspart and insulin detemir without any OADs. The InsV group received BBT with the same insulin plus vildagliptin 50 mg bid. All the medicines, except OADs, were continuously administered throughout the study period. In both groups, the attending physician adjusted the insulin injection dose to maintain the blood glucose level before each meal to within 90−120 mg/dL. Diabetic retinopathy was evaluated 3 days after admission by an ophthalmologist, and if required, fluorescent fundus angiography and retinal laser photocoagulation were immediately performed.

Biochemical Measurement

PG level was measured using a glucose oxidase method, and HbA_{1c} level was measured using high-performance liquid chromatography. Serum total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C: Cholestest-HDL, Sekisui Medical), TG, and glycated albumin (GA: Lucica GA-L, Asahi Kasei Pharma) levels were measured using enzymatic methods. Serum apolipoprotein levels were measured using immunoturbidimetric methods. Non-HDL-C levels were calculated as TC−HDL-C. 1,5-Anhydro-

Table 1. Baseline characteristics

Parameter	Insulin	Insulin + vildagliiptin	*P* value
Number of patients (male)	19 (10)	19 (9)	NS
Age (years)	58 ± 3	65 ± 3	NS
Duration of diabetes (years)	13 ± 3	9 ± 3	NS
BMI (kg/m^2)	24.1 ± 3	26.0 ± 5.4	NS
FPG (mmol/L)	11.4 ± 0.8	12.4 ± 1.8	NS
HbA_{1c} (%)	11.0 ± 2.1	11.1 ± 1.8	NS
GA (%)	31.8 ± 2	32.2 ± 2	NS
ALT (mg/dL)	34 ± 26	31 ± 32	NS
AST (mg/dL)	40 ± 39	32 ± 25	NS
GGT (mg/dL)	90 ± 115	48 ± 35	NS
Cre (mg/dL)	0.67 ± 0.17	0.71 ± 0.21	NS
U-CPR (μg/day)	93.5 ± 17	89.0 ± 16.3	NS
Complication			
Absent Achilles tendon reflex (n)	11	12	NS
U-Alb (mg/day)	46.8 ± 80	54.2 ± 88.2	NS
Diabetic retinopathy (DR)			NS
none (n)	10	9	
simple DR (n)	1	3	
preproliferative DR (n)	1	3	
proliferative DR (n)	4	1	
Medication before admission			NS
sulfonylureas (n)	2	4	
sulfonylureas + biguanides (n)	1	2	
sulfonylureas + thiazolidinediones (n)	1	0	
alpha-glucosidase inhibitors (n)	0	1	
statins (n)	2	1	

Data are expressed as mean ± standard deviation. BMI: body mass index, FPG: fasting plasma glucose, HbA_{1c}: hemoglobin A_{1c}, GA: glycated albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma glutamyl transpeptidase, Cre: creatinine, U-CPR: urinary C-peptide immunoreactivity

glucitol (1,5AG) levels were measured using an enzymatic, colorimetric assay (Lana 1,5AG auto liquid; Nippon Kayaku, Tokyo, Japan). The plasma lipoprotein lipase (LPL) mass and serum ApoB48 levels[33] were measured using an enzyme-linked immunosorbent assay (Daiichi Pure Chemicals and Fujirebio, Tokyo, Japan, respectively). RemL-C levels were measured using a homogenous assay (MetaboRead, Kyowa Medex)[34]. Serum and urine C peptide levels were measured using an electrochemiluminescence immunoassay (Roche Diagnostics, Tokyo, Japan).

Statistical Analysis

All analyses were performed using the JMP 11.0 software (SAS Institute, Cary, NC). Values are presented as mean ± SD. Statistical analyses of gender differences, diabetic complications, and OADs at baseline were performed using the χ^2 test or Fisher's exact test, as appropriate. One-way analysis of variance (ANOVA) and Tukey's honestly significant difference tests with or without Bonferroni correction were used to analyze baseline characteristics and treatment response, as appropriate. Repeated multivariate ANOVA (MANOVA) was used to analyze the daily profiles of PG and serum lipids. $P<0.05$ or $P<0.0125$ was considered as significant.

Results

Subject Recruitment and Clinical Characteristics

A total of 59 patients with type 2 diabetes were assessed for eligibility, and 38 eligible patients (66.7% men; age, 62 ± 3 years; body mass index, 25.1 ± 4.8 kg/m^2; diabetes duration, 11 ± 3 years; HbA_{1c}, 11.0 ± 1%; GA, 32.0 ± 2%; and urinary CPR, 91.1 ± 16.7 μg/day) were selected. Three patients dropped out from each group because of the detection of malignancy, withdrawal of approval, or CGMS recording error (**Fig. 1**). There were no clinically relevant differences in demographic and baseline characteristics between

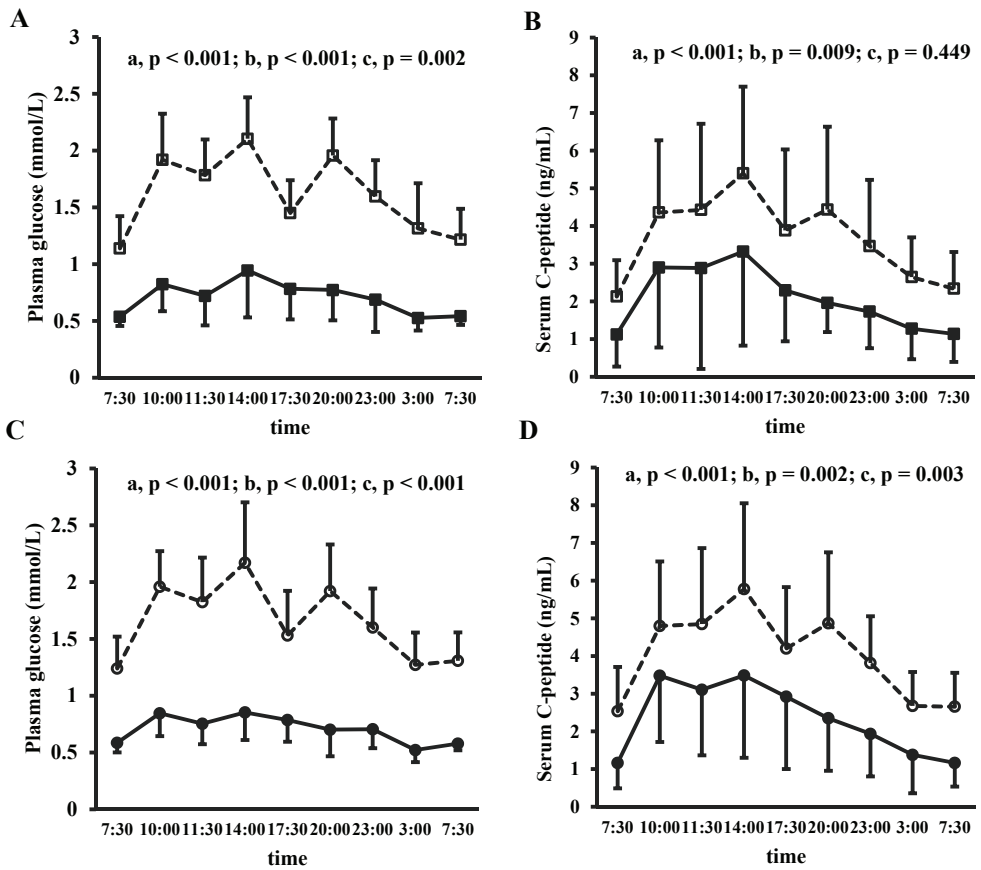

Fig. 2. Daily profiles of plasma glucose and C-peptide

Daily profiles of plasma glucose (A, C) and C-peptide (B, D) on admission (open mark and dotted line) and at discharge (filled mark and solid line) in the insulin group (A, B, squares; $n=16$) and the insulin plus vildagliptin group (C, D, circles; $n=16$).

Data are expressed as mean ± standard deviation. *P* value represents difference according to over time course (a), treatment (b), and the interaction of time course and treatment (c) as calculated using repeated multivariate analysis of variance.

the two groups (**Table 1**).

Effect of Vildagliptin Addition to BBT on Glycemic Control

The daily profiles of PG and CPR on admission and at discharge are shown in **Fig. 2**. The area under the curve (AUC) of PG and CPR at discharge was significantly decreased compared with that on admission in both groups (Ins group: PG, 69% decrease; $P<0.001$ and CPR, 45% decrease; $P=0.006$ and InsV group: PG, 58% decrease; $P<0.001$ and CPR, 42% decrease; $P=0.002$; **Table 2**), but no significant difference was observed in AUC of PG and CPR on admission (PG, $P=0.59$; CPR, $P=0.702$) or at discharge (PG, $P=0.403$; CPR, $P=0.721$) between the two groups.

The duration of hospitalization and HbA_{1c}, GA, 1,5AG, and mean glucose levels calculated using CGM at discharge did not significantly differ between the groups. However, CGM SD, and CGM MAGE were significantly lower in the InsV group than in the Ins group (**Table 2**). Prandial insulin dosage to maintain the pre-meal glucose level within the normal range was 30% lower in the InsV group than in the Ins group, but there was no difference in basal insulin dosage between the two groups.

Change in Lipid Metabolism between Admission and Discharge

Only one and two patients in the InsV and Ins groups, respectively, received statin administration. No one received antidyslipidemic agents except statins administration. Serum lipid (TC, TG, HDL-C, LDL-C, RemL-C, and non-HDL-C) and apolipoprotein (Apo AⅠ, ApoAⅡ, and ApoB) levels were not significantly decreased; however, apolipoproteins (ApoCⅡ, ApoCⅢ, and ApoE) existing on the surface of TG-rich

Table 2. Parameters of glycemic control and insulin dose at discharge

	Insulin			Insulin + vildagliiptin			Ins vs. InsV on admission *P* value	Ins vs. InsV at discharge *P* value
	On admission	At discharge	*P* value	On admission	At discharge	*P* value		
n	16			16				
Duration of hospitalization (days)		14 ± 3			14 ± 2			NS
Insulin aspart (U)		27 ± 2			20 ± 2			0.018
Insulin detemir (U)		11 ± 2			12 ± 2			NS
Daily profile								
AUC of PG (h mmol/L)	38.8 ± 1.4	16.9 ± 1.4	< 0.001	39.5 ± 1.5	16.8 ± 1.5	< 0.001	NS	NS
M-value	91.4 ± 50.6	13.1 ± 7.1	< 0.001	86.2 ± 36	8.1 ± 5.2	< 0.001	NS	NS
AUC of CPR (h ng/mL)	89 ± 9.4	49.3 ± 9.4	0.006	96.5 ± 8.3	55.6 ± 8.3	0.002	NS	NS
CGM								
mean (mg/dL)		135 ± 21			128 ± 15			NS
SD (mg/dL)		40 ± 21			23 ± 12			0.032
MAGE (mg/dL)		112 ± 58			68 ± 15			0.013

Data are expressed as mean ± standard deviation. Bonferroni correction was used in the statistical analysis of the daily profile.
PG: plasma glucose, AUC: area under the curve, CGM: continuous glucose monitoring system, SD: standard deviation, and MAGE: mean amplitude of glycemic excursions

Table 3. Change in serum lipids

	Insulin			Insulin + vildagliiptin			Ins vs. InsV on admission *P* value	Ins vs. InsV at discharge *P* value
	On admission	At discharge	*P* value	On admission	At discharge	*P* value		
TC (mmol/L)	5.1 ± 1.2	4.4 ± 1	NS	5.4 ± 0.9	4.9 ± 0.6	NS	NS	NS
HDL-C (mmol/L)	1.2 ± 0.3	1.1 ± 0.2	NS	1.2 ± 0.2	1.1 ± 0.3	NS	NS	NS
TG (mmol/L)	1.6 ± 0.7	1.1 ± 0.4	NS	1.8 ± 1.1	1.2 ± 0.5	NS	NS	NS
LDL-C (mmol/L)	3.2 ± 1	2.7 ± 0.6	NS	3.4 ± 0.7	3.0 ± 1	NS	NS	NS
Non HDL-C (mmol/L)	3.9 ± 1.2	3.3 ± 1	NS	4.2 ± 0.9	3.6 ± 0.7	NS	NS	NS
ApoAⅠ (mg/dL)	125 ± 27	109 ± 20	NS	121 ± 14	108 ± 13	NS	NS	NS
ApoAⅡ (mg/dL)	26 ± 4	22 ± 4	NS	26 ± 3	22 ± 5	NS	NS	NS
ApoB (mg/dL)	102 ± 35	84 ± 28	NS	110 ± 24	98 ± 23	NS	NS	NS
ApoCⅡ (mg/dL)	5.4 ± 2.1	3.9 ± 1.3	0.007	5.9 ± 2.6	4.3 ± 2.1	0.003	NS	NS
ApoCⅢ (mg/dL)	10.4 ± 3.6	6.3 ± 1.3	< 0.001	11 ± 5	7.2 ± 2	0.011	NS	NS
ApoE (mg/dL)	4.8 ± 1.2	3.9 ± 0.8	0.004	4.9 ± 1.2	4 ± 0.7	0.009	NS	NS
ApoB48 (μg/mL)	4.4 ± 3.4	3.7 ± 2	NS	3.9 ± 2.8	4.3 ± 2	NS	NS	NS
RemL-C (mg/dL)	8.1 ± 4.4	5.4 ± 2.8	NS	10.5 ± 5.4	7.8 ± 2.8	NS	NS	NS
LPL (ng/mL)	57 ± 22	66 ± 28	NS	65 ± 23	64 ± 23	NS	NS	NS

Data are expressed as mean ± standard deviation. Bonferroni correction was used in all statistical analysis.
TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, TG: triglyceride, LDL-C: low-density lipoprotein cholesterol, Apo: apolipoprotein, RemL-C: remnant lipoprotein-cholesterol, LPL: lipoprotein lipase

lipoproteins (TGRL), except ApoB48, were significantly decreased at discharge compared with admission in both groups (**Table 3**). However, there were no significant differences between the groups on admission or at discharge in any parameter. The LPL mass did not show a significant increase with the improvement in glycemic control in either group. The phenotype of ApoE was not significantly different between the two groups. In the Ins group, one patient had E3/2 and another had E3/4. In the InsV group, two patients had E3/2 and two had E3/4. All other patients had E3/3 (data not shown).

The daily profiles and AUC of serum TG and RemL-C indicated that the levels at discharge were significantly lower than those on admission, but no differences were observed between the two groups on

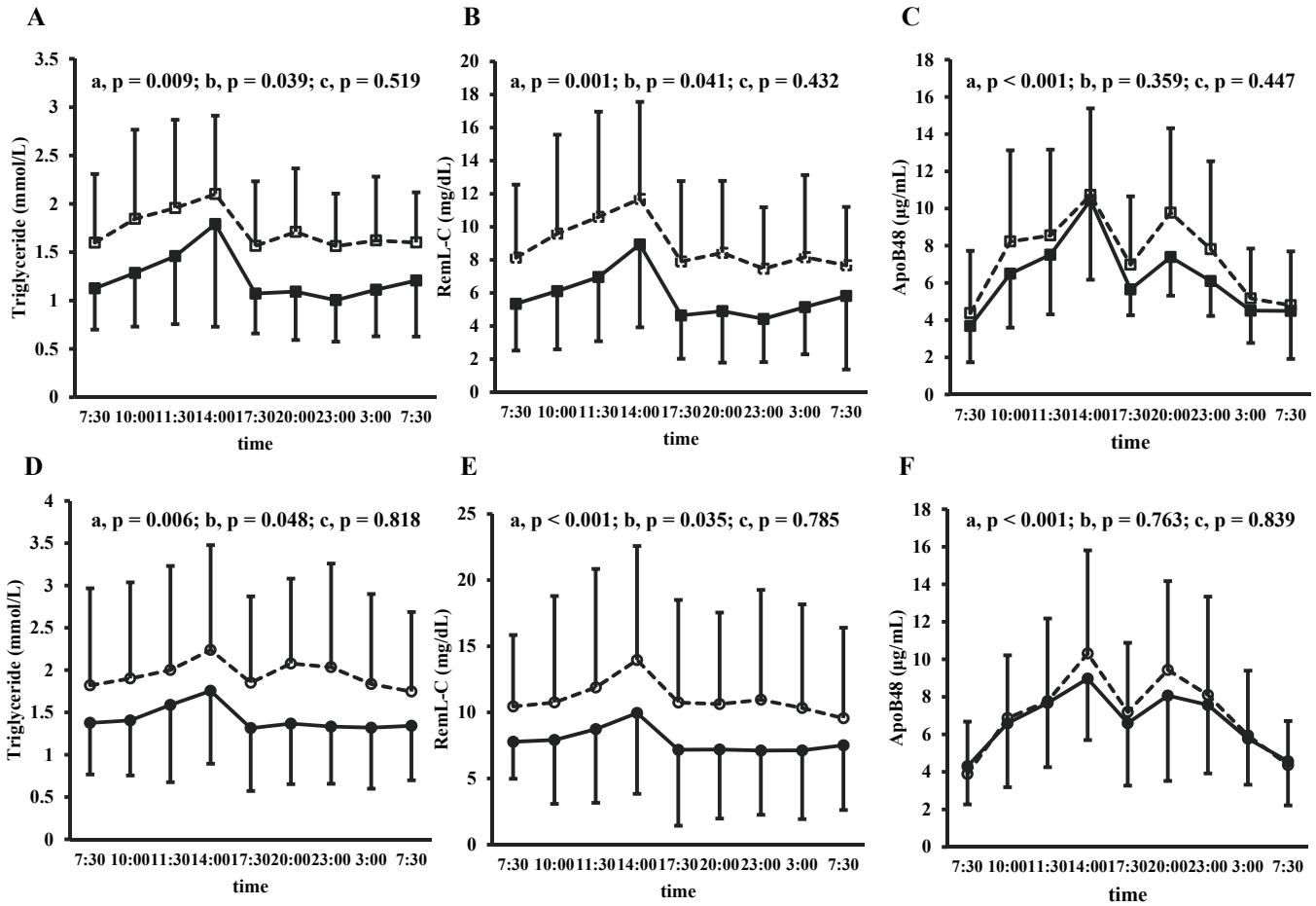

Fig. 3. Daily profiles of serum triglyceride, apolipoprotein B48, and remnant lipoprotein-cholesterol

Daily profiles of serum triglyceride (A, D), remnant lipoprotein-cholesterol (B, E), and Apo B48 (C, F) on admission (open mark and dotted line) and at discharge (filled mark and solid line) in the insulin group (A, B, C; squares) and insulin plus vildagliptin group (D, E, F; circles). Data are expressed as mean ± standard deviation. *P* value represents difference according to the time course (a), treatment (b), and the interaction of time course and treatment (c) as calculated using repeated multivariate analysis of variance.
RemL-C: remnant lipoprotein-cholesterol, ApoB48: apolipoprotein B48

admission or at discharge (**Fig. 3A**, **3B**, **3D**, **3E**, and **Table 4**). No significant changes in serum ApoB48 levels were observed in either group (**Fig. 3C**, **3F**, and **Table 4**). The changes in serum ApoB48 levels from fasting to the peak of the daily profile (2 h after lunch) were significantly smaller in the InsV group at discharge (ApoB48: 4.5 ± 2.5, **Table 4**) than in the Ins group at discharge (ApoB48: 6.8 ± 2.3, $P = 0.012$, **Table 4**). However, the increment in the daily profiles of serum TG and RemL-C was not significant between on admission and at discharge or between the treatment groups.

Correlation between Postprandial Glucose Fluctuation and Postprandial Increment of TGRL-related Parameters

CGM SD and CGM MAGE, indicating glucose fluctuation, were correlated with the postprandial elevation of serum ApoB48 level from fasting to the peak of the daily profile (2 h after lunch) in the Ins group but not in the InsV group and were not correlated with the elevation of serum TG and RemL-C levels (**Fig. 4**) in either of the treatment groups. CGM mean glucose level was not correlated with postprandial increments of TG, RemL-C, and ApoB48 levels.

Discussion

For the first time, we examined the effect of glycemic control with BBT with or without vildagliptin on PG levels and serum triglyceride metabolism and the correlation between postprandial metabolism of PG and serum CM in patients with type 2 diabetes. Our results showed the following: 1) short-term glyce-

Table 4. Change in TG-rich lipoproteins-related parameters during daily profile

	Insulin			Insulin + vildagliiptin			Ins vs. InsV on admission *P* value	Ins vs. InsV at discharge *P* value
	On admission	At discharge	*P* value	On admission	At discharge	*P* value		
AUC								
TG (h mmol/L)	41.3 ± 15.9	29.5 ± 12.5	0.011	46.9 ± 25.7	30 ± 16.7	0.012	NS	NS
RemL-C (h mmol/L)	210.7 ± 111.1	127.1 ± 82.4	0.009	265.6 ± 185	156.3 ± 123	0.01	NS	NS
ApoB48 (h μg/mL)	179.2 ± 89.7	151.9 ± 50.3	NS	176.1 ± 91.8	165.1 ± 71.3	NS	NS	NS
Increment (7:30 − 10:00)								
TG (mmol/L)	0.3 ± 0.3	0.2 ± 0.3	NS	0.1 ± 0.2	0.1 ± 0.2	NS	NS	NS
RemL-C (mmol/L)	1.5 ± 2.1	0.7 ± 0.5	NS	0.3 ± 1.1	0.1 ± 1.4	NS	NS	NS
ApoB48 (μg/mL)	3.9 ± 2.2	2.8 ± 1.4	NS	3 ± 1.6	2.3 ± 2.1	NS	NS	NS
Increment (7:30 − 12:00)								
TG (mmol/L)	0.4 ± 0.3	0.3 ± 0.5	NS	0.2 ± 0.2	0.2 ± 0.5	NS	NS	NS
RemL-C (mmol/L)	2.5 ± 2.6	1.5 ± 1.8	NS	1.4 ± 1.4	0.9 ± 2.6	NS	NS	NS
ApoB48 (μg/mL)	4.2 ± 0.6	3.8 ± 0.6	NS	3.9 ± 2.1	3.4 ± 2.4	NS	NS	NS
Increment (7:30 − 14:00)								
TG (mmol/L)	0.5 ± 0.3	0.7 ± 0.9	NS	0.4 ± 0.3	0.4 ± 0.4	NS	NS	NS
RemL-C (mmol/L)	3.6 ± 2.2	3.3 ± 2.2	NS	3.5 ± 1.6	2.2 ± 2.3	NS	NS	NS
ApoB48 (μg/mL)	6.4 ± 2.2	6.8 ± 2.3	NS	6.4 ± 4	4.5 ± 2.5	NS	NS	0.012

Data are expressed as mean ± standard deviation. Bonferroni correction was used in all statistical analysis.
TG: triglyceride, RemL-C: remnant lipoprotein-cholesterol, ApoB48: apolipoprotein B48

mic control with BBT and a strictly controlled diet decrease the daily profiles of serum TG and RemL-C but not ApoB48 levels and 2) daily glucose fluctuation profile is significantly correlated with the postprandial increment of serum ApoB48 levels.

In this study, vildagliptin addition improved the daily glucose fluctuation profile estimated using CGM. Previous reports have demonstrated that in patients with type 2 diabetes treated with BBT, DPP-4I or the short-acting GLP-1 receptor agonist exenatide ameliorate glycemic control and decrease the prandial (but not basal) insulin dose[35, 36]. GLP-1 enhances glucose-stimulated insulin secretion from pancreatic beta cells *in vitro*[37]. However, in our study, vildagliptin did not significantly increase serum CPR levels under the same blood glucose level as insulin therapy alone. In patients with type 2 diabetes, inappropriately increased glucagon secretion in the postprandial state also causes postprandial hyperglycemia[38, 39], and incretin administration promotes optimal glucagon secretion. Incretins have the potential to slow the rate of absorption of nutrients by decreasing gastric emptying in patients with type 2 diabetes[26]. Through these mechanisms, vildagliptin administration might ameliorate postprandial hyperglycemia without a significant increase in endogenous insulin secretion. The expression of GLP-1 and GIP receptors was reportedly decreased in the pancreatic islets of hyperglycemic rats and recovered when glucose levels were normalized by phlorizin[40]. In patients with type 2 diabetes, sitagliptin decreased prandial insulin dose by approximately 8% and the mean value of HbA_{1c} to 7.3%[36]. We speculate that the greater control of PG achieved in our study enhanced the effects of incretins and caused a larger decrease in prandial insulin dose (26%) observed following vildagliptin administration. The larger decrease in insulin dose might lower the frequency of hypoglycemia, thus helping in decreasing the incidence of dementia[41].

Hyperglycemia (relative deficiency of insulin action) usually elevates TG level; glycemic control decreases this elevation[42]. In this study, fasting serum Apo CⅡ, Apo CⅢ, and ApoE, which exist on the surface of TGRL, levels and the daily profiles of serum TG and RemL-C, which exist in the core of TGRL, levels were significantly decreased after the glycemic control in each group without any increase in the LPL mass. However, the daily profile, including fasting and postprandial state, of serum ApoB48, which was correlated with serum CM particle levels, was not decreased by glycemic control. These data suggest two mechanisms: 1) only VLDL (and VLDL remnant) but not CM (and CM remnant), was hydrolyzed by glycemic control through the independent mechanism of LPL activity and 2) VLDL (and VLDL remnant) and CM (and CM remnant) were hydrolyzed by glycemic control; however, the number of CM (and CM remnant) was not decreased through the independent

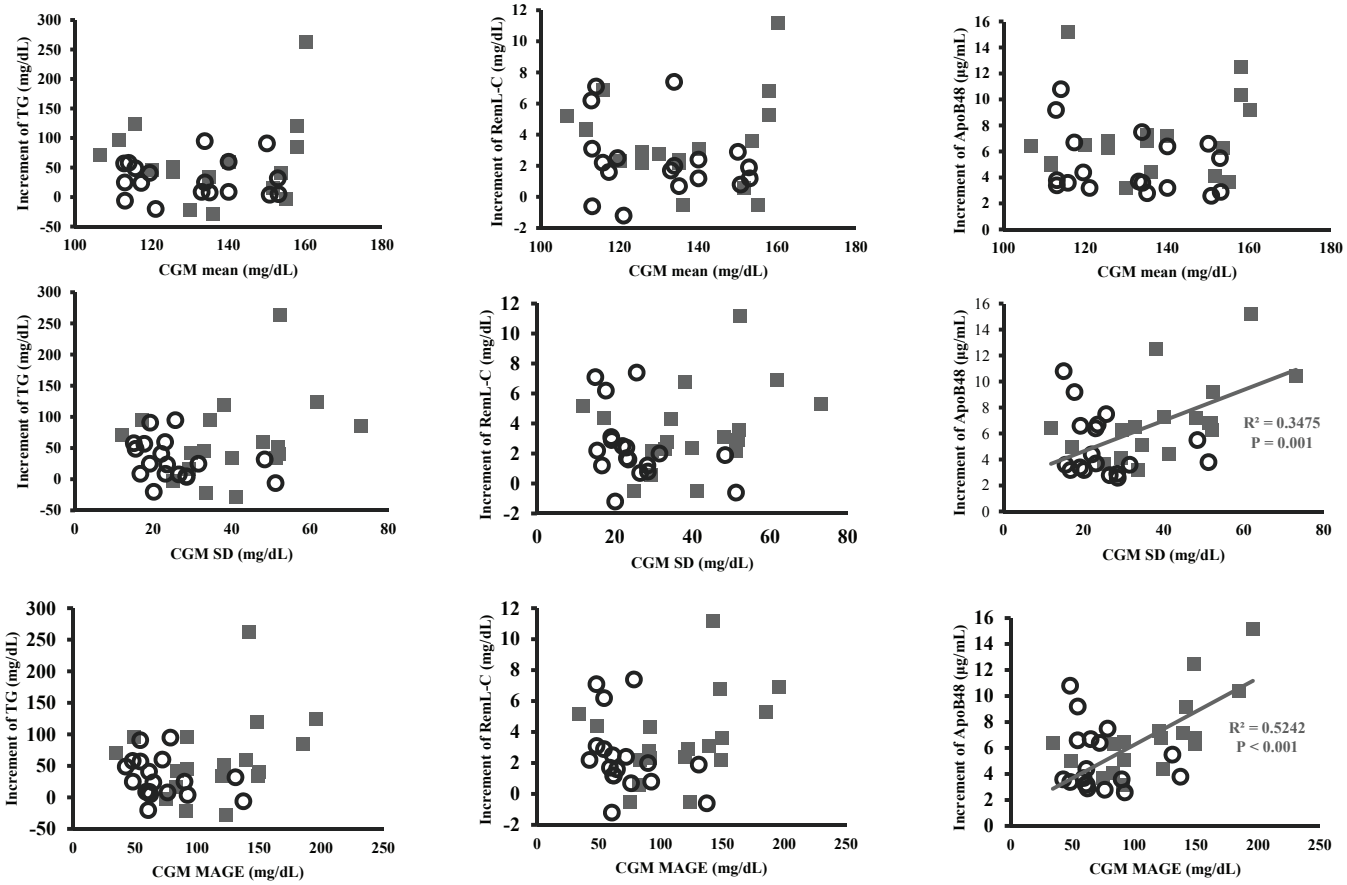

Fig. 4. Correlation between postprandial glucose fluctuation and increment of TG-rich lipoproteins-related parameters

Correlation between postprandial glucose fluctuation and increment of TG-rich lipoproteins-related parameters in the insulin group (filled squares) and insulin plus vildagliptin group (open circles). Increment was calculated by 2 h after lunch−before breakfast in each parameter
TG: triglyceride, RemL-C: remnant lipoprotein-cholesterol, ApoB48: apolipoprotein B48,
CGM: continuous glucose monitoring system, SD: standard deviation, and MAGE: mean amplitude of glycemic excursions

mechanism of LPL activity. If CM (and CM remnant) was hydrolyzed without the decrease in its number, the particle size of CM (and CM remnant) might have decreased. This small-sized CM is considered to be atherogenic.

In this study, LDL-C, HDL-C, and apolipoprotein levels that constitute LDL and HDL, including ApoAI, ApoAII, and ApoB, were also decreased but not significantly in both groups. We previously reported that glycemic control with BBT and a strictly controlled diet in short-term hospitalization significantly decreases LDL-C, HDL-C, TG, and apolipoprotein levels[43], similar to the current study. This decrease might be an effect of the strict diet, but the mechanism remains unclear.

The GLP-1 receptor agonist exenatide suppresses the postprandial production of CMs in the human intestine and reduces the increment of CM particle levels[27]. GLP-1 receptor agonists and/or DPP-4Is can decrease the postprandial elevation of serum TG and ApoB48 levels in patients with type 2 diabetes[28-30]. Similar to previous studies, serum ApoB48 and RemL-C levels at 2 h after lunch (14:00, the peak of the daily profile) tended to be lower in the InsV group than in the Ins group in this study; this difference reached a statistical significance when levels before breakfast were considered.

The daily glucose fluctuation profile estimated using CGM was significantly correlated to the increment of serum ApoB48 levels from fasting to the peak of the daily profile in only the Ins group at discharge. Vildagliptin administration considerably decreased the postprandial PG elevation estimated using CGM and marginally decreased the postprandial serum ApoB48 elevation. Furthermore, vildagliptin administration eliminated the correlation between the postprandial elevation of PG and serum ApoB48. These data suggest that the common mechanism between the post-

prandial metabolism of PG and serum ApoB48 is not the incretin effect.

In conclusion, vildagliptin administration with BBT decreases postprandial PG and serum CM levels in patients with type 2 diabetes. However, short-term glycemic control with BBT alone decreases serum TG and RemL-C levels but not ApoB48 levels in the fasting and postprandial state. Moreover, there is a correlation between postprandial elevation of PG and CM; however, the mechanism remains unclear. To ameliorate both postprandial hyperglycemia and hypertriglyceridemia, basic and clinical investigations for the mechanism of this correlation are required.

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Human Rights Statement and Informed Consent

This single-center, randomized, open-label, controlled study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the local ethics committee of the Nippon Medical School Chiba Hokusoh Hospital. All subjects provided written informed consent (UMIN000011851).

Conflict of Interest

All authors declare no conflict of interest.

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