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Low-carbohydrate diet by staple change attenuates postprandial GIP and CPR levels in type 2 diabetes patients

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ABSTRACT

Aims: The aim of this study is to investigate the effects of a low-carbohydrate staple food (i.e., low-carbohydrate bread) on glucose and lipid metabolism and pancreatic and enteroendocrine hormone secretion in comparison with meals containing normal-carbohydrate bread, without consideration of the carbohydrate content of the side dishes.
Methods: T2DM patients ($n = 41$) were provided meals containing low-carbohydrate bread (LB) together with side dishes or normal-carbohydrate bread (NB) together with side dishes every other day as a breakfast. Blood glucose levels were evaluated by using a continuous glucose monitoring system; blood samples were collected before and 1 and 2 h after the breakfast.
Results: Postprandial blood glucose levels, plasma insulin, plasma glucose-dependent insulinotropic polypeptide (GIP) and plasma triglyceride were significantly lower and plasma glucagon levels were significantly higher in LB compared with those in NB. Plasma glucagon-like peptide-1 (GLP-1) levels did not differ in the LB and NB groups.
Conclusions: These results indicate that changing only the carbohydrate content of the staple food has benefits on glucose and lipid metabolism in T2DM patients concomitant with the decrease of insulin and GIP secretion, which ameliorate body weight gain and insulin resistance.

1. Introduction

Postprandial hyperglycemia is one of major risk factors for cardiovascular disease and mortality both in non-diabetic individuals and diabetic patients.[1–4] Among nutrients, carbohydrates induce elevation of postprandial glucose levels and serum insulin levels.[5] Thus, food nutrients including carbohydrate play an important role in ameliorating glucose excursions. There are several reports describing decreased postprandial glucose levels by dietary intervention in T2DM patients,[6–9] which include reduction of the amount of carbohydrate intake, eating of low glycemic index (GI) foods, meal sequencing and increasing the amount of fiber.

Pancreatic-gastrointestinal hormones such as insulin, glucagon, glucagon-like-peptide 1 (GLP-1), and gastric inhibitory polypeptide (GIP) regulate glucose metabolism.[10,11] These hormones are secreted by nutrients. Glucose stimulates insulin secretion from pancreatic β-cells; oral administration of glucose stimulates GIP secretion from enteroendocrine K-cells and GLP-1 secretion from enteroendocrine L-cells.[10] Glucose suppresses glucagon secretion in non-diabetic subjects, but it slightly promotes glucagon secretion in individuals with Type 2 diabetes (T2DM).[12,13] In addition, oral administration of a protein-rich diet potently stimulates glucagon secretion, and oral administration of fat strongly stimulates GIP secretion.[5,8]

The Japanese diet consists of a staple food consisting mainly of carbohydrate (i.e., rice or bread) and side dishes (i.e., meat, fish, eggs and vegetables), but it is not understood whether simply reducing the carbohydrate content of the staple food can elicit beneficial changes in postprandial glucose levels and pancreatic gastrointestinal hormone secretion. In the present study, we investigated whether a low-carbohydrate diet derived from changing the staple food from normal-carbohydrate bread to low-carbohydrate bread

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affects postprandial glucose and lipid metabolism and pancreatic gastrointestinal hormone secretion.

2. Materials and methods

2.1. Subjects

T2DM patients ($n = 41$) who were hospitalized in Fujita Health University Hospital from February to September 2018 were enrolled in the present study. Eligible patients were age 20–80 years and showed fasting plasma glucose levels below 11.1 mM 3 days before the beginning of the study. The patients enrolled in the study were expected not to change their glucose-lowering medication or dose of insulin during the study. In case a patient needed to change medication, they were excluded from the study. The study protocol was approved by the Ethics Committee of Fujita Health University (HM 17-154; UMIN registration: UMIN 00003010). All patients provided written informed consent.

2.2. Study design

The patients were subjected to 24 h continuous glucose monitoring (CGM) (Libre Pro® Medtronic) for 7 days (3 days before initiation of the study to day 4 of the study). The subjects received breakfast at 0800, lunch at 1200 and dinner at 1800. On day 1 and 3, they received normal-bread (NB) with side dishes and on day 2 and 4 they received low-carbohydrate bread (LB) with side dishes at 0800 as breakfast. NB (185 kcal) contained 32.7 g carbohydrate (dietary fiber, 1.6 g); protein, 6.5 g; and fat, 3.1 g. LB (187.8 kcal) contained 20.7 g carbohydrate (dietary fiber, 11.1 g); protein, 17.4 g; and fat, 6.0 g. NB with side dishes (total 490 kcal) consisted of carbohydrate, 48.8%; protein, 15.8%; and fat, 35.4%. LB with side dishes (total 476.2 kcal) consisted of carbohydrate, 35.5%; protein, 21.5%; and fat, 43.0%.

2.3. Biochemical analyses

Blood samples were collected before and 1 and 2 h after breakfast on day 3 and 4. Hormones were measured using the following assays as described previously[14]: Total GLP-1, Human Total GLP-1 (ver. 2) assay kit (catalogue number K150JVC-2; Mesoscale Discovery, Gaithersburg, MD, USA); Total GIP, Human GIP (total) ELISA (Catalogue Number EZHGIP-54K; Merck Millipore, Darmstadt, Germany); Glucagon, glucagon ELISA kit (Catalogue Number 10-1281-01; Mercodia, Uppsala, Sweden).[15] Other laboratory measurements including insulin were done by standard assay at SRL, Tokyo, Japan.

2.4. Statistical analysis

Data are presented as means ± SEM. Statistical significance was evaluated by paired *t*-test using JMP version 8.0 (SAS Institute, Cary, NC, USA). A probability level of $P < 0.05$ was considered statistically significant.

3. Results

3.1. Characteristics of subjects

A total of 41 T2DM patients were enrolled in the study. Six patients were excluded because of inability to collect blood samples for biochemical analyses, 5 patients were excluded because data of CGM could not be obtained, 1 patient was excluded because of non-completion of the breakfast, and 1 patient was excluded due to change of glucose-lowering medication during the trial. Finally, 28 subjects with T2DM completed the study (Fig. 1). The average age of the participants was 65.0 ± 11.0 years, body mass index (BMI) was 25.1 ± 4.97 (kg/m^2), HbA1c levels were 8.74 ± 2.31%, and estimated glomerular filtration rate (eGFR) was 72.3 ± 20.4 (ml/min/1.73 m^2) (Table 1). Additional information regarding glucose-lowering medications is described in Table 1.

3.2. The effect of LB on postprandial blood glucose levels

We first investigated whether dietary intervention of LB decreased postprandial glucose concentrations and the duration of any effects of LB on glucose concentrations. LB decreased postprandial glucose levels after breakfast, but not after lunch (Fig. 2.A, B). $tAUC_{0-240}$ of glucose concentrations after breakfast in the LB group were significantly lower than those in the NB group, while $tAUC_{0-240}$ of glucose concentrations after lunch did not differ in the NC and LB groups (Fig. 2.C).

3.3. The effect of LB on hormonal change

We next assessed the effect of LB on pancreatic and enteroendocrine hormone secretion. Plasma C-peptide hormone immunoreactivity (CPR) levels were significantly lower at 2 h after breakfast, and plasma glucagon levels were significantly higher at 1 and 2 h after breakfast in the LB group compared with those in the NB group (Fig. 3.A, B). On the other hand, plasma GIP levels were significantly lower at 1 h after breakfast and tended to be lower at 2 h after breakfast ($P = 0.17$) in the LB group compared with those in the NB group (Fig. 3.C). However, plasma GLP-1 levels were the same in the NB and LB groups after breakfast (Fig. 3.D).

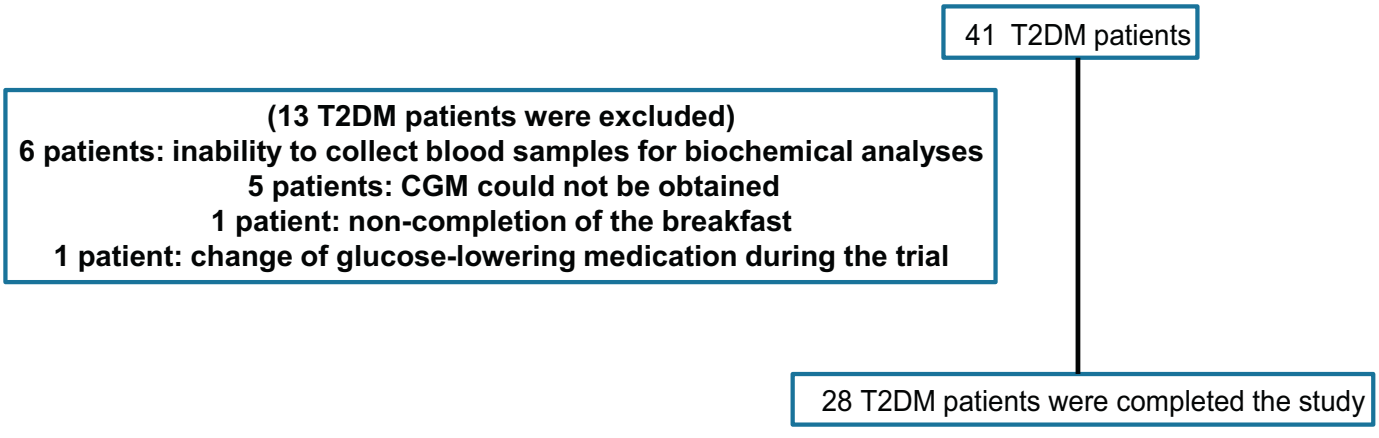

Fig. 1. Flow chart of subjects.

Table 1
Characteristic of participants in with T2DM at baseline.

		Mean ± SD
Age (year)		65.0 ± 11.0
Gender (male/female)		M20/F8
BH (cm)		163.2 ± 8.7
BW (kg)		67.2 ± 19.4
BMI (kg/m^2)		25.1 ± 4.9
HbA1c		8.74 ± 2.31
eGFR		72.3 ± 20.4
Treatment for type 2 diabetes		
Oral anti diabetic agent	Sulfonylureas	5 (17.8%)
	Glinides	4 (14.2%)
	Biguanides	13 (46.4%)
	Thiazolidinediones	5 (17.8%)
	α-Glucosidase inhibitors	7 (25.0%)
	DPP-4 inhibitors	19 (67.8%)
	SGLT2 inhibitors	9 (32.1%)
GLP-1 receptor agonist		4 (14.2%)
Insulin		5 (17.8%)

Data are expressed as mean ± standard deviation or number (n).
BH, body height; BW, body weight; BMI, body mass index;
eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c.
DPP-4, dipeptidyl peptidase-4; SGLT2, sodium glucose cotransporter 2.

3.4. The effect of LB on lipid profile

We then evaluated the effect of LB on postprandial lipid profile. Plasma triglyceride levels were significantly lower at 2 h after breakfast in the LB group compared with those in the NB group (Fig. 4.A). Plasma low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol and free fatty acid (FFA) levels did not differ in the NB and LB groups (Fig. 4.B, C, D).

4. Discussion

In the present study, we show that changing only the staple food from NB to LB, which changes the carbohydrate content from 48.8% to 35.5% of total calories in the meal, decreased postprandial plasma glucose and triglyceride levels. Concomitantly, postprandial plasma GIP and CPR levels were significantly decreased and the plasma glucagon levels were significantly increased by switching from normal-carbohydrate bread to low-carbohydrate bread in T2DM patients in the present study, despite their taking diabetic medications.

Obesity is associated with increased risk of cardiovascular disease, cancer, T2DM and insulin resistance.[16,17] Also, in diabetes patients, a high incidence of macrovascular disease and cancer is serious problem. Administration of a low-carbohydrate diet leads to long-term weight loss.[18] Furthermore, intervention of a low-carbohydrate diet suppresses postprandial glucose levels and improves glycemic control in T2DM patients.[6,19–21] It is therefore considered that intervention of a low-carbohydrate diet has a benefit not only on glucose metabolism, but also in extending life expectancy by reducing the incidence of diabetic complications such as macrovascular disease and cancer. However, it is difficult for an individual to prepare every meal in consideration of the percentage of carbohydrate. It may be easier to choose a staple food containing a lower percentage of carbohydrate rather than attempting to prepare side dishes containing a lower percentage of carbohydrate. We therefore investigated glucose metabolism and lipid metabolism in a low-carbohydrate diet by changing the staple food from normal-carbohydrate bread to low-carbohydrate bread. In our previous study, dietary intervention of low-carbohydrate intake in total energy elicited reduced postprandial glucose levels in impaired glucose regulation (IGR) and T2DM patients, but the glucose lowering effect by the low-carbohydrate diet was weak in normal glucose tolerance (NGT) subjects.[19,22,23] On the other hand, intervention of a low-carbohydrate

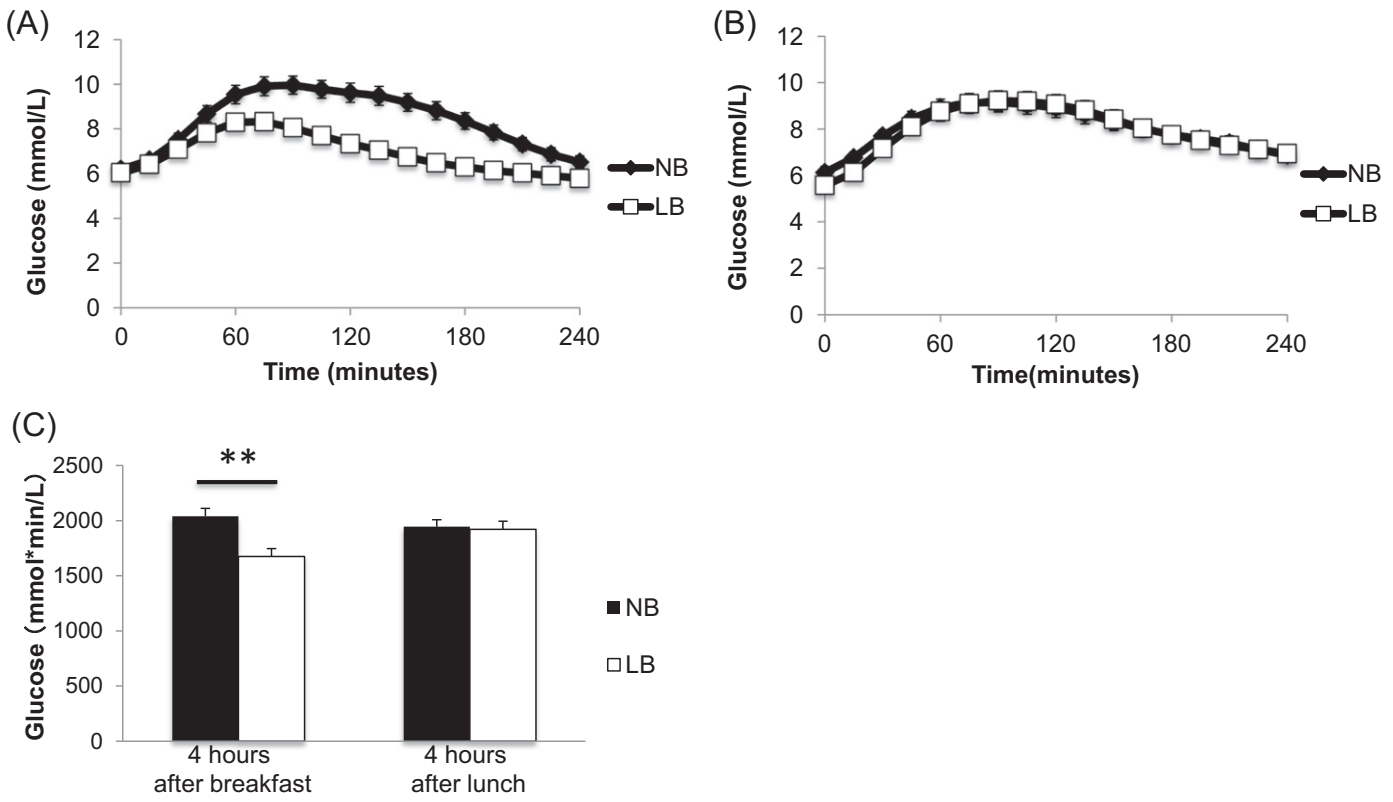

Fig. 2. Postprandial glucose concentrations. (A) Postprandial glucose concentration after breakfast assessed by continuous glucose monitoring (CGM). Normal-bread group (NB) (black squares); low-carbohydrate bread group (LB) (white squares). (B) Postprandial glucose concentration after lunch assessed by CGM. NB (black square), LB (white square). (C) tAUC of postprandial glucose levels for 4 h after breakfast and after lunch. NB (black bar), LB (white bar) is LB. (**$P < 0.01$). Data represent means ± SEM.

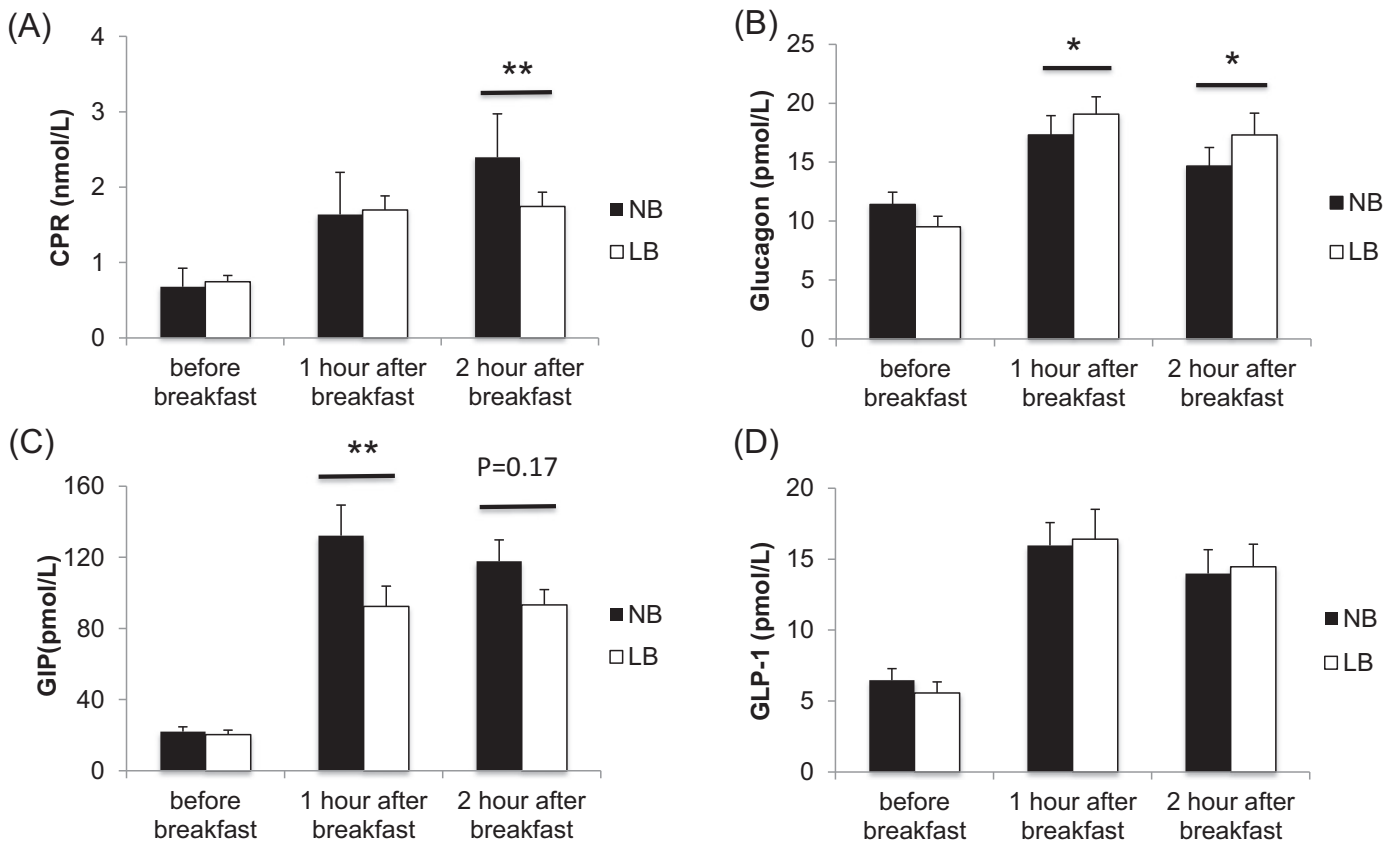

Fig. 3. Postprandial plasma pancreatic enteroendocrine hormone levels (A) CPR, (B) glucagon, (C) GIP, (D) GLP-1. Normal-bread group (NB) (black bar); low-carbohydrate bread group (LB) (white bar). (*$P < 0.05$, **$P < 0.01$) Data represent means ± SEM.

diet decreases postprandial plasma insulin levels both in NGT subjects and T2DM patients.[6,19] In the present study, we show that breakfast with low-carbohydrate bread reduced postprandial glucose levels concomitantly with decreasing postprandial plasma CPR levels in Japanese T2DM patients, who are characterized by diminished β-cell function and lesser obesity and higher insulin sensitivity compared with Caucasian.[24]

GIP-secreting K-cells occur predominantly in upper intestine; GLP-1-secreting L-cells occur predominantly in lower intestine.[25] Both GIP and GLP-1 potentiate glucose-induced insulin secretion. GLP-1 contributes to weight loss by reducing food intake and/or slowing gastric empting. On the other hand, GIP participates in body weight gain by promoting uptake of glucose and fat into adipose tissue synergistically with insulin, and is involved in insulin resistance.[10,26,27] Interestingly, in the present study, postprandial plasma GIP levels were decreased in patients taking low-carbohydrate bread. This result is coincident with previous reports of dietary intervention of a low percentage of carbohydrate in total kilocalories in NGT subjects.[23] Plasma GIP levels are higher in subjects with normal glucose tolerance after oral mixed meal containing 57.8 g carbohydrate and 16.6 g fat than those after 75 g oral glucose administration[28], indicating that an equal amount of fat more strongly stimulates GIP secretion than that of carbohydrate. On the other hand, administration of both carbohydrate and fat potently stimulates GIP secretion, while protein does not induce GIP secretion in healthy human subjects.[5] In the present study, in LB, the total amount of carbohydrate and fat that stimulates GIP secretion may be less than that in NB due to the increase in the amount of protein comprising the total of nutrients. Thus, plasma GIP levels are lower in LB group than those in NB group not only due to the lower amount of carbohydrate content, but also partly and indirectly to the higher protein content.

Although we previously reported that insulin rather than GIP plays an important role in high-carbohydrate-induced obesity and enhanced insulin secretion in mice[29,30], whether or not the reduction of GIP secretion participates in the decrease of insulin secretion and/or the increase of insulin sensitivity in T2DM patients taking low-carbohydrate bread or long-term intake of low-carbohydrate bread contributes to weight loss and improved glucose metabolism should be investigated in future.

Low-carbohydrate diets result in a higher proportional intake of protein and fat. Plasma triglyceride levels increase linearly with the amount of fat in adults[31]. Indeed, postprandial plasma triglyceride levels are elevated after intake of low-carbohydrate diet.[19,20] In the present study, postprandial plasma triglyceride levels were decreased after meal in the low-carbohydrate group. In addition, GLP-1 infusion was found to inhibit postprandial plasma triglyceride levels in rodents and T2DM patients, presumably due to suppression of apolipoprotein B-48 secretion.[32–34] In the present study, postprandial plasma GLP-1 levels did not differ in those taking meals with low-carbohydrate bread and normal-carbohydrate bread. Thus, GLP-1 may not be involved in the improved lipid metabolism in T2DM patients taking low-carbohydrate bread. Plasma glucagon levels are increased by administration of a protein-rich diet, along with a decrease in insulin action.[8,11,35,36] In addition, glucagon decreases plasma triglyceride levels due to increasing FFA beta oxidation, and reduces triglyceride synthesis in mice.[37] Whether the elevation of glucagon secretion in patients taking low-carbohydrate bread is due to decreased insulin secretion or intake of a protein-rich diet is not known, but enhanced glucagon secretion might contribute partially to the decrease in postprandial triglyceride levels in T2DM patients taking low-carbohydrate bread.[6,19]

A fiber-rich diet decreases postprandial glucose levels, accompanied by a decline of postprandial insulin levels in T2DM patients, and reduces the risk of coronary heart disease.[9,38,39] In addition, a fiber-rich diet reduces postprandial triglyceride levels in T2DM patients.[38,40] A glucose or fat-rich diet is known to induce induces oxidative stress and

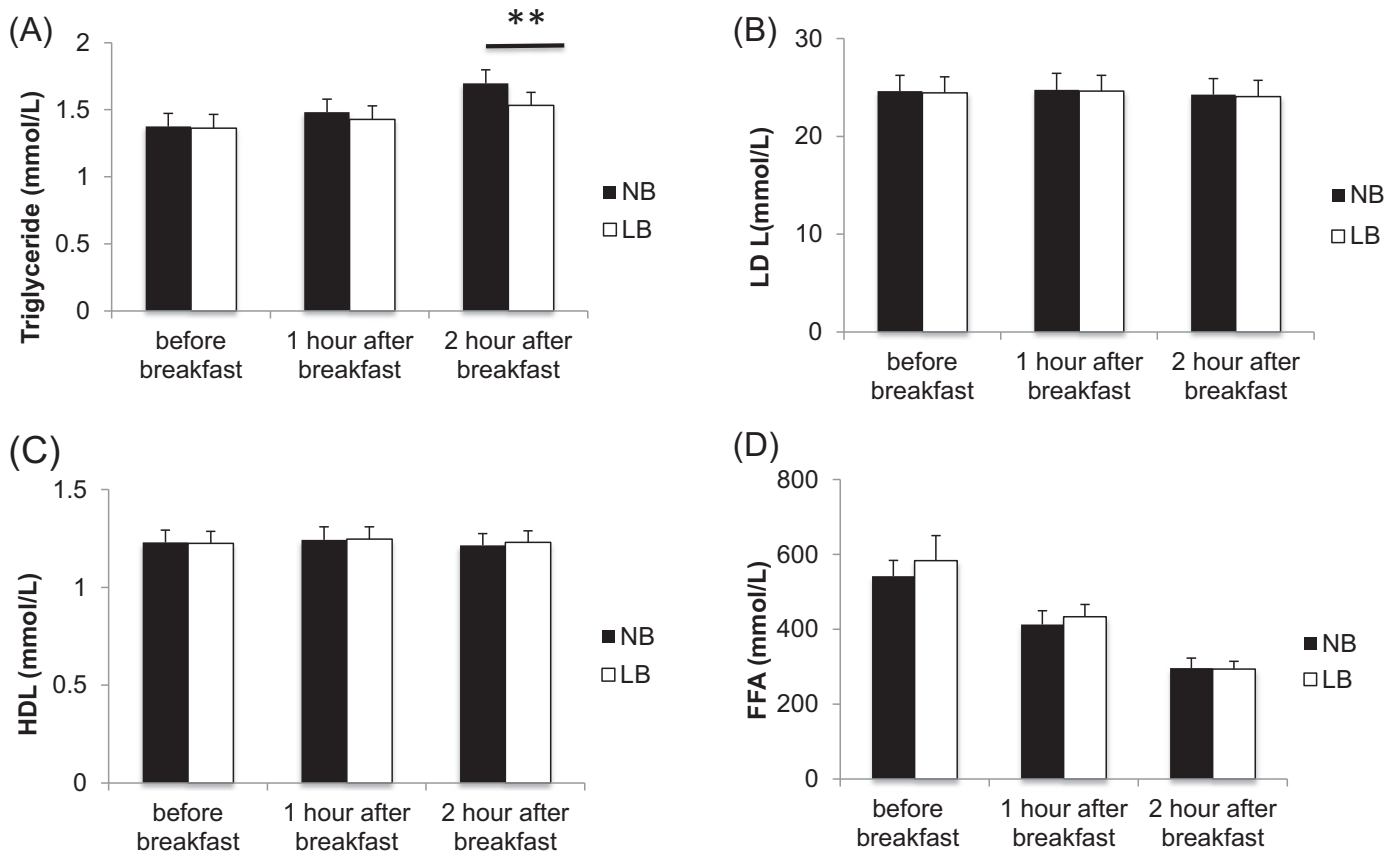

Fig. 4. Postprandial plasma lipid profiles (A) triglyceride, (B) LDL, (C) HDL, (D) FFA. Normal-bread group (NB) (black bar); low-carbohydrate bread group (LB) (white bar). (**$P < 0.01$) Data represent means ± SEM.

inflammation.[41,42] Also, the addition of fiber to high-fat high-calorie meal induces the anti-inflammatory effects and also decreases postprandial glucose and triglyceride levels in lean healthy subjects.[42,43] To ascertain whether the lower percentage of carbohydrate or the greater amount of fiber in LB induces the beneficial effects on postprandial oxidative and inflammatory stress and glucose and lipid metabolism requires further investigation.

In conclusion, we found that changing only the carbohydrate content of the staple food has benefits on glucose and lipid metabolism in T2DM patients concomitant with the decrease of insulin and GIP secretion, which ameliorate body weight gain and insulin resistance.

Abbreviations

BMI	body mass index
CGM	continuous glucose monitoring
CPR	C-peptide hormone immunoreactivity
eGFR	estimated glomerular filtration rate
FFA	free fatty acid
IGR	impaired glucose regulation
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
HDL	high-density lipid
LB	low-carbohydrate bread
LDL	low-density lipid
NB	normal-carbohydrate bread
NGT	normal-glucose tolerance
tAUC	total area under the curve
T2DM	type 2 diabetes

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Declaration of competing interest

None.

Ethics

The study protocol was approved by the Ethics Committee of Fujita Health University (HM 17-154; UMIN registration: UMIN 00003010). All patients provided written informed consent.

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