의학박사 학위논문

The Effect of Nutrient Preload on Glucose Tolerance, Appetite, and Food Intake

식전 부하의 내당능, 식욕 및 음식 섭취에 대한 효과 연구

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Major in Translational Medicine

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Abstract

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The unprecedented global epidemic of diabetes mellitus and obesity necessitates more effective prevention and treatment to halt the growing burden of diseases. Nutrition therapy is an essential component of the management of these noncommunicable diseases. Recently, besides meal size and composition, meal timing and the order of eating food have been identified as major determinants of postprandial glycemia and food intake. Thus, the nutritional strategies, such as nutrient preload and manipulation of food order, could be a feasible option for the management of diabetes mellitus and obesity.

Nutrient preload, which refers to the intake of a small amount of food before a meal, using whey protein has reduced postprandial hyperglycemia and food intake in individuals with varying degrees of glucose intolerance. In previous studies, a high dose of protein, usually 50 g, was required to achieve clinically meaningful improvements in hyperglycemia. However, long-term caloric surplus by protein preload might promote weight gain and offset its beneficial effects. In this regard,

we developed a protein-enriched, dietary fiber-fortified bar (PFB), containing 10.7 of protein and 12.7 of dietary fiber, to maintain the metabolic benefits of nutrient preload while decreasing the potential risk of high-dose protein. In the present study, we investigated the effects of the PFB preload on glucose tolerance, appetite, and food intake.

The first study evaluated the effect of premeal PFB on postprandial glucose excursions in 15 individuals with type 2 diabetes and 15 individuals with normal glucose tolerance (NGT). This study was a randomized, open-label, crossover study. The participants consumed the PFB at −30 minutes before (premeal) or immediately after (postmeal) a test meal. Plasma levels of glucose, insulin, and gut hormones were measured during a mixed meal tolerance test. The premeal PFB significantly reduced postprandial hyperglycemia compared with the postmeal PFB in individuals with type 2 diabetes (14,723 ± 1,310 mg·min/dL vs. 19,642 ± 1,367 mg·min/dL, P = 0.0002) and NGT (3,943 ± 416 mg·min/dL vs. 4,827 ± 520 mg·min/dL, P = 0.0296). In individuals with type 2 diabetes, the premeal PFB significantly increased early insulin secretion and enhanced postprandial GLP-1 secretion compared with the postmeal PFB. All participants completed the study with no adverse event.

The second study evaluated the effect of PFB preload on appetite and food intake in 20 healthy individuals. This study was a randomized, open-label, crossover, and exploratory study. After consuming a PFB, usual cereal bar, or water preload at −15 minutes before a test meal in a randomized order, the participants had an *ad libitum* test meal for 120 minutes. The amount of food intake, appetite, fullness, and plasma levels of glucose, insulin, and gut hormones were measured. The PFB preload significantly reduced the total energy intake compared with the

water preload (904.4 ± 534.9 kcal vs. 1,075.0 ± 508.0 kcal, $P = 0.016$). In addition, the PFB preload significantly increased fullness, lowered postprandial glucose levels, and enhanced GLP-1 secretion compared with the other two preloads. All participants completed the study with no adverse event.

In conclusion, premeal consumption of the PFB improved postprandial glucose excursions in individuals with type 2 diabetes and NGT and reduced appetite and food intake in healthy individuals with changes in gut hormones, which might be beneficial to the management of diabetes mellitus and obesity.

Keywords : Appetite, Dietary fiber, Energy intake, Gastrointestinal hormones, Postprandial hyperglycemia, Whey proteins

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Introduction

1. The importance of nutrition therapy in postprandial glycemic control

Diabetes mellitus is one of the major noncommunicable diseases and has become a global health problem (1). Type 2 diabetes, accounting for 90% of all cases, is characterized by dysregulation in glucose homeostasis resulting from insulin resistance and impaired insulin secretion (2). Among risk factors for type 2 diabetes, overweight and obesity are imperative contributors to insulin resistance, which is followed by the progressive decline in beta-cell function (3). The pathogenesis of obesity is complicated, but two main mechanisms are sustained positive energy balance and alteration in body weight set point (4). Unhealthy diets or eating patterns have a large impact on this process and contribute to pathophysiological changes in obesity and type 2 diabetes (4, 5). Therefore, appropriate nutrition therapy is crucial to the management of type 2 diabetes.

Medical nutrition therapy is an individualized intervention to achieve metabolic goals of blood glucose levels, blood pressure, lipid profiles, and excess body weight loss. Although there is no one-size-fits-all eating plan, individuals with or at risk for type 2 diabetes should have a balanced diet that contains an adequate amount of high-quality food (6). Current guidelines recommend that macronutrient composition has no ideal proportions and should be individualized based on metabolic goals, nutritional status, physical activity, eating pattern, personal or cultural preferences, complications, and comorbidities (6, 7). In general, total caloric intake should be reset depending on weight management goals.

Consumption of dietary fiber is encouraged, preferably through food, and the intake of unsaturated fat is emphasized instead of saturated fat and *trans* fat. The usefulness of the glycemic index and glycemic load is uncertain in individuals with or at risk for diabetes mellitus (6). Medical nutrition therapy provided by a registered dietitian or registered dietitian nutritionist reduced a glycosylated hemoglobin (HbA1c) by 1%–2% (6, 8) and decreased body weight by 5% or more in individuals with type 2 diabetes and prediabetes (9, 10). Although the effect of nutrition therapy is clear, it is one of the most difficult parts of the management of diabetes mellitus. More adherent approaches are needed with an understanding of metabolic changes in type 2 diabetes.

Postprandial hyperglycemia is the hallmark of individuals with impaired glucose tolerance (IGT) or early stage of type 2 diabetes (11). IGT is characterized by insulin resistance in muscle and impaired late (second-phase) insulin secretion after a meal, which is different from hepatic insulin resistance and impaired early (first-phase) insulin secretion observed in impaired fasting glucose (2). Epidemiologic studies have revealed that postprandial hyperglycemia is associated with an increased risk of type 2 diabetes, cardiovascular disease, and mortality (12-21). Indeed, antidiabetic therapy targeting postprandial hyperglycemia, such as alpha-glucosidase inhibitors and prandial insulin, reduced the risk for type 2 diabetes (22, 23) and major cardiovascular events (24, 25) in individuals with IGT or type 2 diabetes. Accordingly, postprandial glycemic control is important in individuals with or at risk for diabetes mellitus.

Postprandial glucose levels are determined by numerous factors, including the amount and composition of nutrients, gastric emptying time, intestinal glucose absorption, secretion of gut hormones and insulin, glucose uptake and utilization

by insulin-sensitive tissues, and endogenous glucose production (26). Emerging evidence suggests that, besides meal size or composition, meal timing and the order of eating food regulate postprandial glycemia by affecting these factors (27). Nutrient preload and carbohydrates-last food order improved postprandial glucose excursions through enhancing the secretion of insulin and incretin hormones (28). These nutritional strategies could be effective for the prevention and management of diabetes mellitus and obesity.

2. Evidence of the effect of nutrient preload on glycemic control

Nutrient preload is the consumption of a small amount of food or nutrients at a fixed interval, usually 15 to 30 minutes before a meal. The effect of nutrient preload on insulin and glycemic responses had been previously reported in untreated individuals with type 2 diabetes after the ingestion of milk (29). A study in healthy individuals identified that whey protein, a byproduct of cheese production in milk, had an insulinotropic property and increased the release of glucose-dependent insulinotropic polypeptide (GIP) (30). On the basis of these findings, the metabolic effect of nutrient preload has been evaluated mainly on whey protein.

2.1. Short-term effects of whey preload in individuals with type 2 diabetes

In diet-controlled individuals with type 2 diabetes, 27.6 to 55 g of whey preloads significantly reduced postprandial glucose excursion (31, 32), stimulated the secretion of insulin (31, 32), glucagon-like peptide-1 (GLP-1) (32), GIP (31), and cholecystokinin (32), and slowed gastric emptying (32) compared with placebo

after a mixed meal. Additionally, whey preload enhanced early insulin secretion, increased plasma GLP-1 levels, and slowed gastric emptying when compared with whey consumption with a meal (32). The benefits of a 25-g whey preload on postprandial glycemia and gastric emptying persisted after 4 weeks of exposure in diet-controlled individuals with type 2 diabetes (33).

The favorable effects of whey preload have also been reported in individuals treated with antidiabetic drugs. In metformin-treated individuals, 25 to 50 g of whey preloads significantly reduced postprandial hyperglycemia (34, 35), stimulated insulin secretion (34, 35), increased plasma levels of GLP-1 (34, 35), GIP (35), and glucagon (35), and slowed gastric emptying (35) compared with placebo after a mixed meal. Notably, in individuals who were taking sulfonylurea or metformin, a 50-g whey preload decreased postprandial glucose levels by 28% with a twofold increase in insulin responses, especially early insulin secretion, and augmented GLP-1 responses (34). Although indirectly compared, the glucose-lowering effect of whey preload in this study was greater than that of nateglinide (36), glipizide (37), and glibenclamide (37), and the increase in insulin secretion was similar to that of repaglinide (38). In addition, whey preload enhanced the efficacy of vildagliptin through increasing plasma levels of intact GLP-1 and GIP, suppressing plasma glucagon levels, and slowing gastric emptying in individuals who were taking metformin (35).

2.2. Long-term effects of whey preload in individuals with type 2 diabetes

There are insufficient data for determining the long-term effects of whey preload in individuals with type 2 diabetes. In individuals treated with diet or

metformin, 12 weeks of nutrient preload that contained 17 g of whey protein and 5 g of guar had sustained effects of slowing gastric emptying (189 ± 7 minutes vs. 167 ± 5 minutes, $P < 0.05$) and a 15% decrease in postprandial hyperglycemia with a modest HbA1c reduction (6.6 ± 0.05% vs. 6.7 ± 0.05%, $P < 0.05$) and no weight gain compared with placebo (39). Whey protein/guar preload showed significantly lower postprandial GLP-1 responses and higher levels of plasma glucagon than placebo at both week 1 and week 12. Plasma insulin levels were not different between the groups throughout the study (39).

2.3. Effects of whey preload in individuals with gestational diabetes mellitus and normoglycemia

Macronutrient preload, containing 7.5 g of protein from whey, pea, and egg, significantly lowered fasting blood glucose and 2-hour postprandial blood glucose levels compared with milk powder in individuals with gestational diabetes mellitus (40). The mean duration of intervention was 65 days, and neonatal birth weight and delivery mode were not different between the groups (40).

In individuals with normoglycemia, 9 to 40 g of whey preloads lowered postprandial glucose levels and enhanced insulin secretion in a dose-dependent manner (41, 42) after a mixed meal. It also increased plasmas levels of GLP-1 (41, 42) and peptide YY (PYY) (43) and slowed gastric emptying (44).

2.4. Effects of protein and lipid preload on glucose tolerance

Several studies have reported that nutrient preload with a small amount of protein and lipid improves postprandial glucose excursions. A preload, consisting

of 50 g of parmesan cheese and 50 g of egg, improved glucose tolerance after a 75-g oral glucose tolerance test in individuals with normal glucose tolerance (NGT), IGT, and type 2 diabetes (45). The beneficial effects on glucose intolerance increased with higher degrees of glucose tolerance impairment (NGT −32%, IGT −37%, and type 2 diabetes −49%, $P < 0.002$) (45). Rate of the appearance of oral glucose and rate of the glucose absorption were leading contributors with a small increase in GLP-1 and GIP responses (45). In individuals with type 2 diabetes, a protein and lipid preload improved glucose intolerance mainly by reducing appearance of oral glucose, improving beta-cell function, and reducing insulin clearance (46).

3. Evidence of the effect of the order of eating food on glycemic control

Carbohydrates are dietary components that have the greatest influence on blood glucose levels (47). Carbohydrates-last food order is a simple way to improve postprandial hyperglycemia by manipulating the sequence of macro-nutrient ingestion with no significant change in eating patterns (48).

3.1. Short-term effects of carbohydrates-last food order in individuals with type 2 diabetes

In metformin-treated individuals with type 2 diabetes, the ingestion of protein and vegetables before carbohydrates significantly improved postprandial hyper-glycemia by 53% with lower insulin (49, 50) and higher GLP-1 excursions (50)

compared with carbohydrates-first food order.

In Japanese individuals not treated for type 2 diabetes, the ingestion of fish before rice or meat before rice improved postprandial hyperglycemia and glycemic variability compared with the ingestion of rice before fish (51). The ingestion of fish before rice or meat before rice also delayed gastric emptying and increased the secretion of GLP-1 and glucagon (51). Postprandial GLP-1 secretion was greater in the meat before rice than in the fish before rice (51), which suggests that protein intake may have different effects depending on its types or compositions.

3.2. Long-term effects of carbohydrates-last food order in individuals with type 2 diabetes and NGT

The 8 weeks of ingestion of lipid and protein before carbohydrates significantly reduced fasting blood glucose levels (−1.8 mmol/L vs. −0.3 mmol/L, $P < 0.01$), postprandial hyperglycemia (−3.2 mmol/L vs. −0.4 mmol/L, $P < 0.01$), and a HbA1c level (−0.5% vs. −0.2%, $P < 0.04$) with lower glycemic variability (standard deviation −0.7 mmol/L vs. −0.2 mmol/L, $P < 0.02$) compared with carbohydrates-first food order in individuals with type 2 diabetes under free-living conditions (48). These patients were taking metformin and/or sitagliptin for the treatment of type 2 diabetes. There was no difference in body weight and lipid profiles between the procedures (48).

Eating vegetables before carbohydrates significantly improved postprandial glucose excursions and glycemic variability, assessed by a continuous glucose monitoring system, in Japanese individuals with type 2 diabetes and NGT (52). The mean amplitude of glycemic excursions were 4.36 ± 1.86 mM vs. 6.52 ± 3.17 mM

($P < 0.01$) and 1.56 ± 0.74 mM vs. 2.44 ± 1.09 mM ($P < 0.01$) in individuals with type 2 diabetes and NGT, respectively. These beneficial effects were observed for 2.5 years in both two groups (52).

3.3. Effects of carbohydrates-last food order in individuals with prediabetes

The ingestion of protein and vegetables before carbohydrates significantly reduced postprandial hyperglycemia by 39% compared with carbohydrates-first food order in individuals with prediabetes (53). Carbohydrates-last food order also showed stable postprandial glucose levels which was different from marked glycemic variability in carbohydrates-first food order (53).

3.4. Long-term effects of carbohydrates-last food order in individuals with type 1 diabetes

In individuals with type 1 diabetes aged 7 to 17 years, the intake of protein and fat prior to carbohydrates significantly improved postprandial glucose excursions with no difference in mean and peak glucose levels compared with the intake of macronutrients altogether (54). There was no difference in the number and time to onset of hypoglycemic events between the groups (54).

Hypothesis of the Study

The nutrient preload containing a modest amount of protein and dietary fiber will improve postprandial glucose excursion and decrease appetite and food intake by affecting gut hormones.

Chapter 1.

Postprandial glucose-lowering effect of premeal consumption of protein-enriched, dietary-fiber fortified bar in individuals with type 2 diabetes and normal glucose tolerance

Introduction

A protein preload has the glucose-lowering and insulinotropic effects in individuals with type 2 diabetes and NGT (27, 28). Nonetheless, the optimal dose of protein in nutrient preload has not been determined. In individual with type 2 diabetes, a 50 g of whey protein was required to demonstrate significant improvement in postprandial hyperglycemia (34). However, 50 g of protein corresponds to 200 kcal and long-term caloric surplus by protein preload might promote weight gain and offset its beneficial effects in some people.

Dietary fiber can be a good supplement to protein preload. The ingestion of dietary fiber improves postprandial glycemia by reducing caloric intake, increasing satiety, and slowing gastric emptying (55-57). The glucose-lowering effect of dietary fiber has been inconsistently reported with a mean change in HbA1c of −0.55% (95% confidence interval −0.96% to −0.31%) (58). In addition, there are a few results of the effect of dietary fiber preload on postprandial glycemia. In individuals with prediabetes and type 2 diabetes, nutrient preload that contained 17 g of whey protein and 5 g of guar decreased peak and 3-hour glucose levels after a mixed meal (59). Therefore, the addition of dietary fiber to protein preload might be a plausible option to preserve its glucose-lowering effect while reducing the amount of protein.

In this regard, we developed a protein-enriched, dietary fiber-fortified bar (PFB) as nutrient preload (Patent number: 10-2016-0093458, PCT/KR2016/009958); (ⅰ) to decrease the amount of protein and caloric intake, (ⅱ) to obtain metabolic benefits of dietary fiber, (ⅲ) to reduce the cost of production, and (ⅳ) to improve palatability. In the present study (60), we investigated the glucose-

lowering effect of premeal PFB compared with that of postmeal PFB in individuals with type 2 diabetes and NGT.

Methods

Study participants

A total of 30 individuals (15 with type 2 diabetes and 15 with NGT) were included in the present study. Eligible participants were individuals aged 18 to 80 years with a body mass index (BMI) of 18.5–35.0 kg/m^2, an estimated glomerular filtration rate of ≥ 30 mL/min/1.73 m^2, and aspartate aminotransferase and alanine aminotransferase levels of ≤ 2.5-fold the upper limit of normal range. Individuals with type 2 diabetes had clinically diagnosed with type 2 diabetes at least 12 weeks before the screening and were treated with lifestyle management and/or oral antidiabetic drugs, including metformin, sulfonylurea, and dipeptidyl peptidase-4 (DPP-4) inhibitor as monotherapy or combination therapy. In individuals with type 2 diabetes, a HbA1c was 6.5%–10.0% if they were drug-naïve, 6.0%–10.0% if they were taking metformin or sulfonylurea, and 6.0%–9.0% if they had taken DPP-4 inhibitor as combination therapy for at least 12 weeks before randomization. Individual with NGT had never been diagnosed with diabetes mellitus, and had fasting plasma glucose levels < 100 mg/dL and a HbA1c level < 6.0% according to the National Institute for Health and Care Excellence Guidance for Type 2 Diabetes Mellitus (61). We excluded individuals who were diagnosed with type 1 diabetes; had a history of diabetic ketoacidosis; were undergoing insulin therapy; had a history of allergy to flour, nuts, legumes, and milk; had history of gastrointestinal surgery except appendectomy, hernia repair surgery, and hemorrhoidectomy; and women who were pregnant or lactating.

Ethical statement

The study protocol was approved by the institutional review board of Seoul National University Hospital (IRB No. 1504-103-666) and registered at ClinicalTrial.gov (ClinicalTrails.gov Identifier: NCT02589028). All participants provided written informed consent.

Study design and procedures

The present study was a randomized, open-label, crossover study. Eligible participants visited the Clinical Trial Center of Seoul National University Hospital at 08:30 hour after an overnight (10-hour) fast on 2 separate days, 1 week apart. The participants were randomly assigned to two groups and consumed a PFB before (premeal PFB) or after breakfast (postmeal PFB) with a mixed meal tolerance test (MMTT). In the premeal PFB group, the participants started to consume the PFB at −30 min (08:30 hour) before eating the teat meal (09:00 hour). In the postmeal PFB group, the participants started to eat the test meal at 0 min (09:00 hour) and consume the PFB at the end of the test meal. The PFB was provided with 150 mL of water. The participants were instructed to consume the test meal and PFB, both within 15min. After 1 week, the participants were offered the PFB and test meal in reverse order (Fig. 1). The participants stopped taking metformin or sulfonylurea the day before the first visit and DPP-4 inhibitor 1 week before the first visit.

The PFB was made by Ssial Food Inc. (Jecheon, Chungcheongbuk-do, Korea). One serving of PFB (30 g) had 73 kcal and contained 0.4 g of carbohydrates, 9.3 g of whey protein, 1.4 g of soy protein, 0.3 g of fat, and 12.7 g of dietary fiber. The ingredients of the PFB were whey protein (36.7%), soy protein nuggets (5.4%),

acacia gum (24.6%), indigestible maltodextrin (25.8%), D-sorbitol (6.4%), stevia (0.6%), glycerin fatty acid esters (0.4%), citric acid (0.1%), and vanilla extract (0.1%). The test meal was a standardized diet with a high glycemic index. Nutrition facts of the PFB and test meal are detailed in Table 1.

Figure 1. Study design and procedures. Study participants were randomly assigned to two groups and consumed the PFB before or after breakfast (test meal) with a MMTT in a crossover design. PFB, protein-enriched, dietary fiber-fortified bar; MMTT, mixed meal tolerance test; GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide.

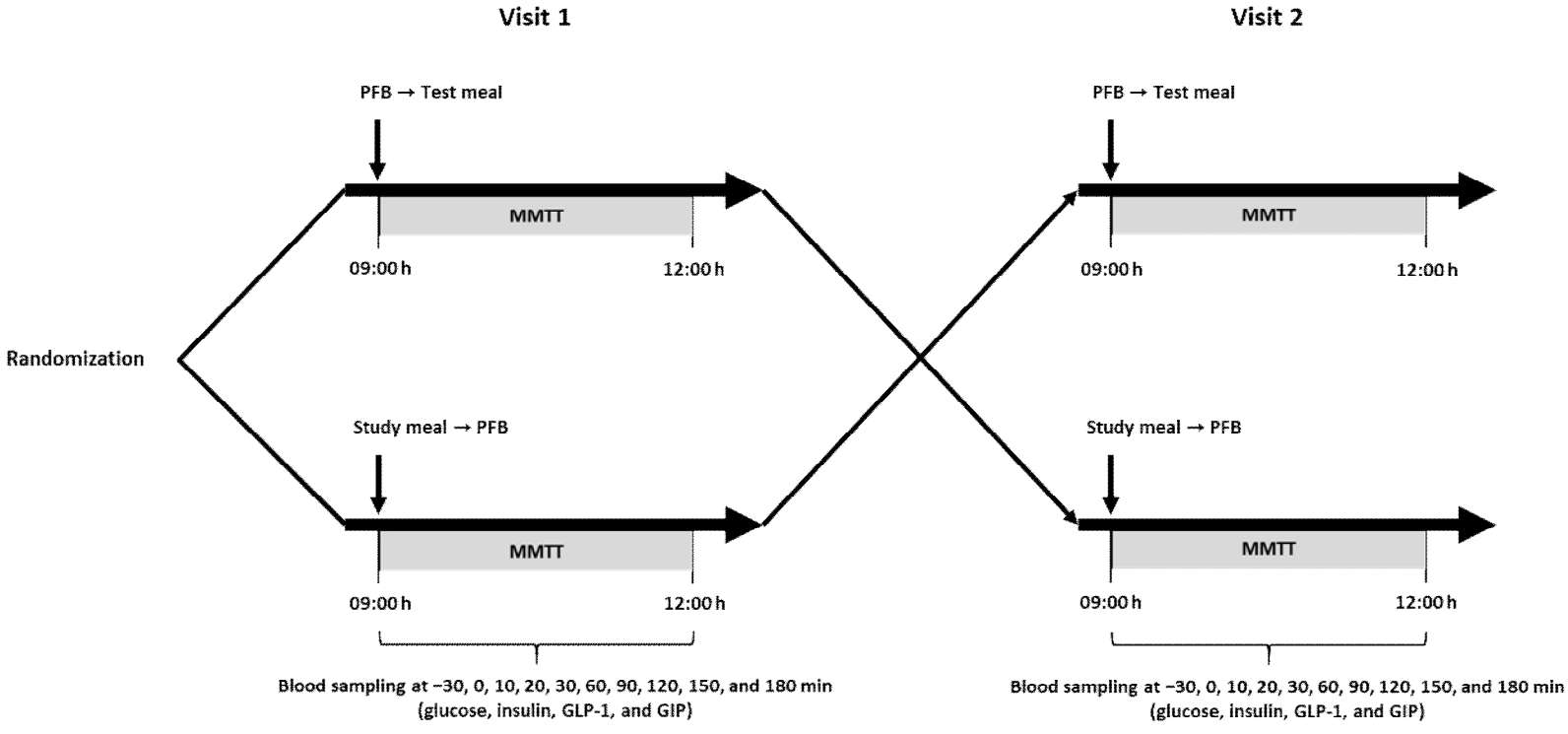


Table 1. Nutrition facts of the PFB and test meal

	PFB	Test meal		
		Bagel	Cream cheese	Orange juice
Amount, g	30.0	100.0	70.0	210.0
Energy, kcal	73.0	286.0	217.0	95.0
Carbohydrates, g	0.4	55.0	3.5	21.0
Protein, g	10.7	10.0	3.5	2.0
Fat, g	0.3	29.0	21.0	0.5
Dietary fiber, g	12.7	–	–	–

PFB, protein-enriched, dietary-fiber fortified bar.

Measurements

An 18-gauge indwelling intravenous catheter was placed in the forearm. Venous samples were collected at −30, 0, 10, 20, 30, 60, 90, 120, 150, and 180 minutes during the MMTT. Serum and plasma were separated immediately by centrifugation at 500 *g*, 4℃ for 15 minutes and stored at −70℃ for further analyses.

Plasma glucose concentrations were measured by the glucose oxidase method (YSI 2300 STAT PLUS analyzer; YSI Inc., Yellow Springs, OH, USA). Plasma insulin concentrations were measured by electrochemiluminescence immunoassay (IMMULITE 2000; Siemens, Munich, Germany). Plasma concentrations of total GLP-1 (Alpco Diagnostics, Salem, NH, USA) and total GIP (Millipore, Billerica, MA, USA) were analyzed by enzyme-linked immunosorbent assay. All assays were performed according to the manufacturer's instructions.

Study endpoints

The primary endpoint was the difference in the incremental area under the curve of plasma glucose levels during the 180-minute MMTT ($iAUC_{0\text{-}180}$) between the premeal and postmeal PFB in individuals with type 2 diabetes and NGT. The secondary endpoints were the differences in the $iAUC_{0\text{-}180}$ of plasma levels of insulin, total GLP-1, and total GIP between the premeal and postmeal PFB in individuals with type 2 diabetes and NGT.

Sample size calculation

The number of study participants was determined based on the incremental area under the curve (iAUC) of plasma glucose levels reported in the previous

study (62), assuming a difference of 290 mmol·min/L between the premeal and postmeal PFB with a power of 80% and a type Ⅰ error of 0.05. Considering a dropout rate of 20%, 15 individuals were recruited in the type 2 diabetes and NGT groups, respectively.

Statistical analysis

Continuous variables were presented as mean ± standard deviation or standard error of the mean. Categorical variables are reported as frequencies and proportions. Plasma levels of glucose, insulin, total GLP-1, total GIP, and glucagon from 0 to 180 minutes were analyzed by two-way repeated measures analysis of variance (ANOVA). The iAUC of plasma glucose, insulin, total GLP-1, total GIP, and glucagon levels was calculated according to the trapezoid rule and analyzed by the paired *t*-test. Insulinogenic index (IGI) was calculated as (insulin at 30 minutes – insulin at 0 minutes)/(glucose at 30 minutes – glucose at 0 minutes). All data were analyzed by GraphPad Prism 5 (GraphPad Software Inc., San Diego, CA, USA). *P* values < 0.05 were accepted as statistically significant.

Results

Characteristics of study participants

Among 31 individuals screened for the present study, one individual in the NGT group was excluded because of fasting hyperglycemia. Finally, 30 individuals (15 with type 2 diabetes and 15 with NGT) completed the study with no adverse event, including gastrointestinal disturbance. In individuals with type 2 diabetes, the mean age was 62.9 ± 4.3 years, BMI was 24.8 ± 3.5 kg/m^2, and HbA1c was 6.8 ± 0.4%. The mean duration of type 2 diabetes were 13.8 ± 6.7 years. All the individuals with type 2 diabetes were taking at least on oral antidiabetic drugs, including metformin. In individuals with NGT, the mean age was 47.3 ± 9.8 years, BMI was 23.1 ± 3.1 kg/m^2, and HbA1c was 5.3 ± 0.3%. Baseline characteristics of the participants are described in Table 2.

Table 2. Baseline characteristics of the study participants

	Type 2 diabetes (n = 15)	NGT (n = 15)	P value
Age, years	62.9 ± 4.3	47.3 ± 9.8	< 0.001
Sex, % of men (men/women)	33 (5/10)	47 (7/8)	0.710
Hypertension, n	6	0	< 0.001
Dyslipidemia, n	6	0	< 0.001
Duration of diabetes, years	13.8 ± 6.7	−	NA
Antidiabetic drugs, n	15	0	NA
Metformin alone	7	0	NA
Metformin + SU	4	0	NA
Metformin + DPP-4 inhibitor	2	0	NA
Metformin + SU + DPP-4 inhibitor	2	0	NA
BMI, kg/m^2	24.8 ± 3.5	23.1 ± 3.1	0.161
Fasting plasma glucose, mg/dL	130 ± 30	91 ± 6	< 0.001
HbA1c, %	6.8 ± 0.4	5.3 ± 0.3	< 0.001
Total cholesterol, mg/dL	152 ± 12	208 ± 38	< 0.001
HDL cholesterol, mg/dL	50 ± 15	60 ± 16	< 0.112
LDL cholesterol, mg/dL	79 ± 16	124 ± 38	< 0.001
eGFR, mL/min/1.73 m^2	79.0 ± 18.0	88.9 ± 13.4	0.107
AST, IU/L	22 ± 7	21 ± 5	0.625
ALT, IU/L	21 ± 11	17 ± 7	0.277

Values are presented as mean ± standard deviation and the number or proportions of the participants. NGT, normal glucose tolerance; SU, sulfonylurea; DPP-4 inhibitor, dipeptidyl peptidase-4 inhibitor; BMI, body mass index; HbA1c, glycated

hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; NA, not applicable.

Plasma glucose levels during the 180-minute MMTT

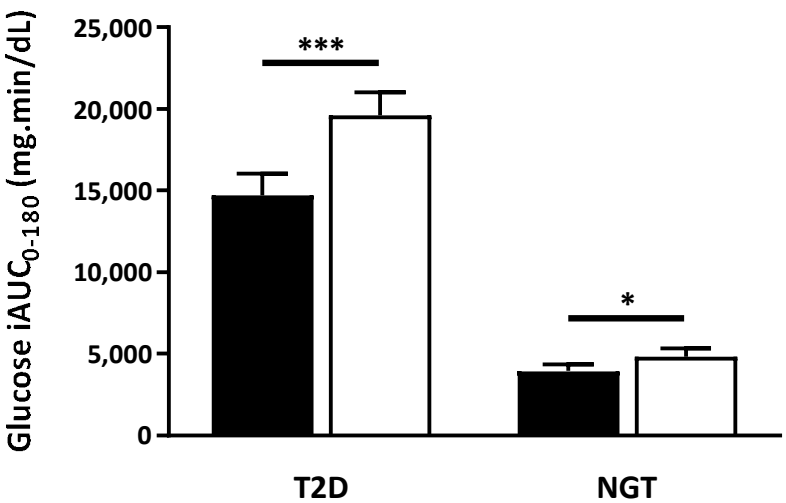
In individuals with type 2 diabetes, the $iAUC_{0\text{-}180}$ of plasma glucose levels was significantly lower with the premeal PFB than with the postmeal PFB (14,723 ± 1,310 mg·min/dL vs. 19,642 ± 1,367 mg·min/dL, $P = 0.0002$) (Fig. 2A). Post-prandial glucose levels tended to be lower with the premeal PFB than with the postmeal PFB (Fig. 2B).

In individuals with NGT, the $iAUC_{0\text{-}180}$ of plasma glucose levels was significantly lower with the premeal PFB than with the postmeal PFB (3,943 ± 416 mg·min/dL vs. 4,827 ± 520 mg·min/dL, $P = 0.0296$) (Fig. 2A). Plasma glucose levels were significantly lower with the premeal PFB than with the postmeal PFB at 30 minutes (122 ± 4 mg/dL vs. 146 ± 5 mg/dL, $P = 0.001$) and 60 minutes (118 ± 5 mg/dL vs. 138 ± 7 mg/dL, $P = 0.007$) after a test meal (Fig. 2C).

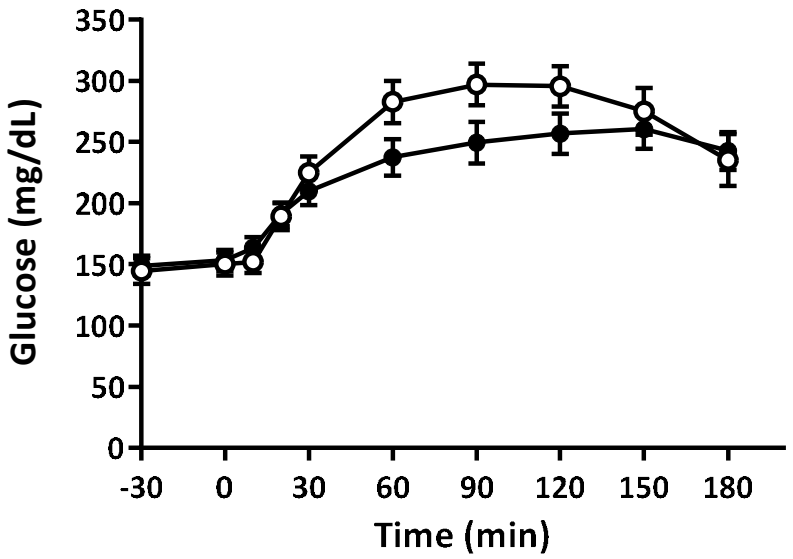
Premeal PFB did not affect plasma glucose levels at 0 minutes in both individuals with type 2 diabetes and NGT.

Figure 2. Postprandial glucose levels during the 180-minute MMTT in individuals with type 2 diabetes and NGT. (A) The $iAUC_{0\text{-}180}$ of plasma glucose levels. (B) Plasma glucose levels in type 2 diabetes. (C) Plasma glucose levels in NGT. Values are presented as mean ± standard error of the mean in the graphs. Black bar/circle, premeal protein-enriched, dietary fiber-fortified bar (PFB); white bar/circle, postmeal PFB. MMTT, mixed meal tolerance test; T2D, type 2 diabetes; NGT, normal glucose tolerance; $iAUC_{0\text{-}180}$, incremental area under the curve during the 180-min MMTT. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

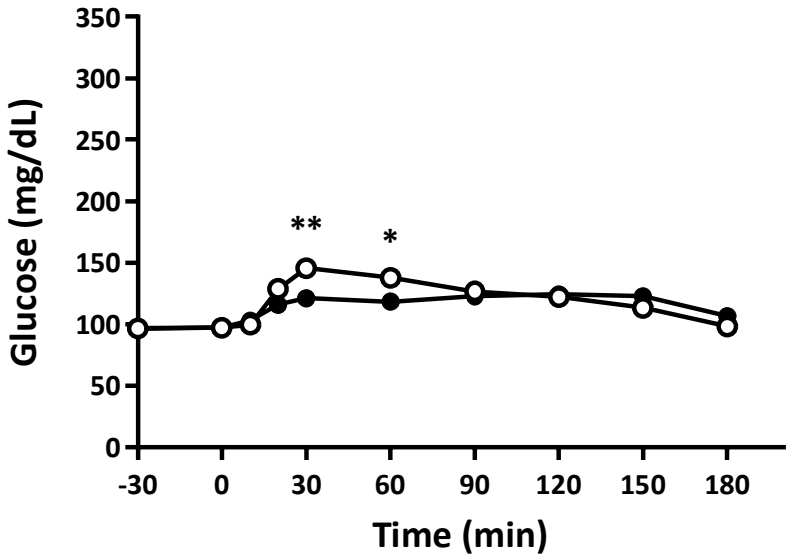
(A)



(B)


Glucose (mg/dL)
350
300
250
200
150
100
50
0
-30
0
30
60
90
120
150
180
Time (min)

(C)


Glucose (mg/dL)
350
300
250
200
150
100
50
0
**
*
-30
0
30
60
90
120
150
180
Time (min)

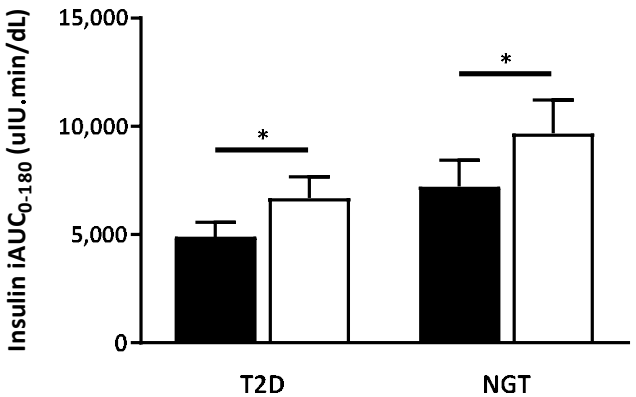
Plasma insulin levels during the 180-minute MMTT

In individuals with type 2 diabetes, the $iAUC_{0\text{-}180}$ of plasma insulin levels was significantly lower with the premeal PFB than with the postmeal PFB (4,898 ± 677 μIU·min/mL vs. 6,680 ± 986 μIU·min/mL, P = 0.0019) (Fig. 3A). Intriguingly, however, the premeal PFB stimulated early insulin secretion, indicated by shifting the insulin curve to the left, compared with the postmeal PFB in individuals with type 2 diabetes (Fig. 3B). The insulin secretion tended to be higher with the premeal PFB in the early postprandial period and lower in the late postprandial period than with the postmeal PFB (Fig. 3B). Plasma insulin levels were significantly lower with the premeal PFB than with the postmeal PFB at 150 minutes after the test meal (39.8 ± 5.0 μIU·min/mL vs. 59.7 ± 8.0 μIU·min/mL, P = 0.001) (Fig. 3B). The IGI was significantly higher with the premeal PFB than with the postmeal PFB (0.53 ± 0.43 vs. 0.28 ± 0.16, P = 0.0166) (Fig. 3D).

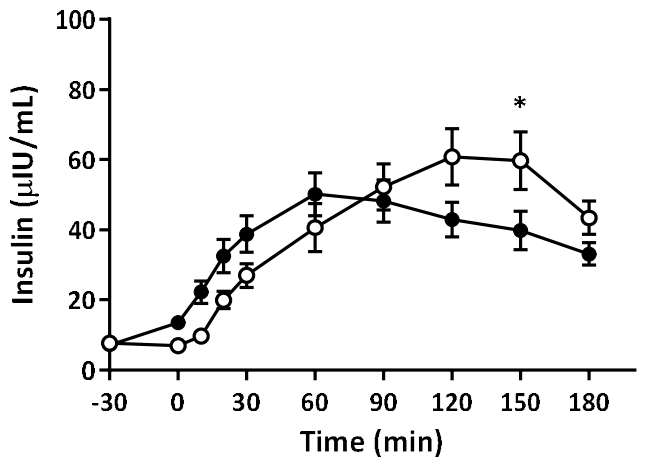
In individuals with NGT, the $iAUC_{0\text{-}180}$ of plasma insulin levels was significantly lower with the premeal PFB than with the postmeal PFB (7,217 ± 1,201 μIU·min/mL vs. 9,664 ± 1,558 μIU·min/mL, P = 0.0039) (Fig. 3A). However, there was no shift in the insulin curve and no difference in the IGI (2.18 ± 0.90 vs. 1.47 ± 0.88; P = 0.4125) between the premeal and postmeal PFB (Fig. 3C and D).

Figure 3. Postprandial insulin levels and the IGI during the 180-minute MMTT in individuals with type 2 diabetes and NGT. (A) The $iAUC_{0\text{-}180}$ of plasma insulin levels. (B) Plasma insulin levels in type 2 diabetes. (C) Plasma insulin levels in NGT. (D) IGI. Values are presented as mean ± standard error of the mean in the graphs. Black bar/circle, premeal protein-enriched, dietary fiber-fortified bar (PFB); white bar/circle, postmeal PFB. MMTT, mixed meal tolerance test; T2D, type 2 diabetes; NGT, normal glucose tolerance; $iAUC_{0\text{-}180}$, incremental area under the curve during the 180-minute MMTT; IGI, insulinogenic index. $^{*}P < 0.05$.

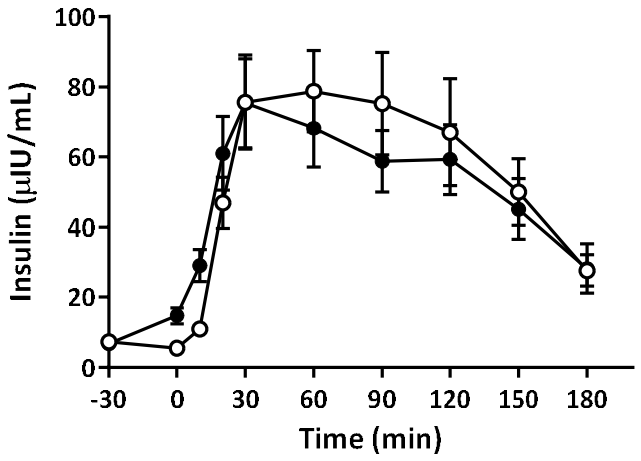
(A)



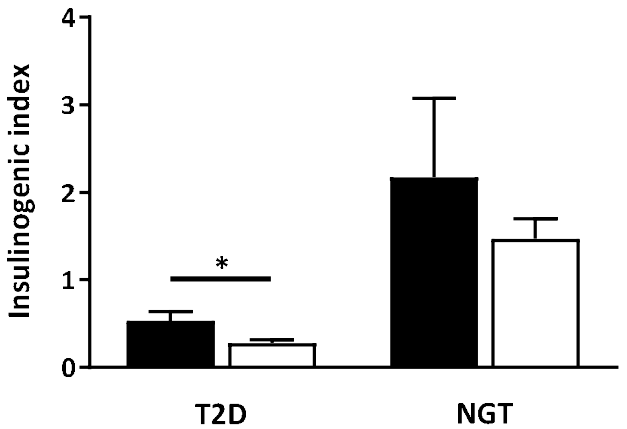
(B)



(C)


100
80
60
40
20
0
Insulin (μIU/mL)
-30
0
30
60
90
120
150
180
Time (min)

(D)


4
3
2
1
0
Insulinogenic index
*
T2D
NGT

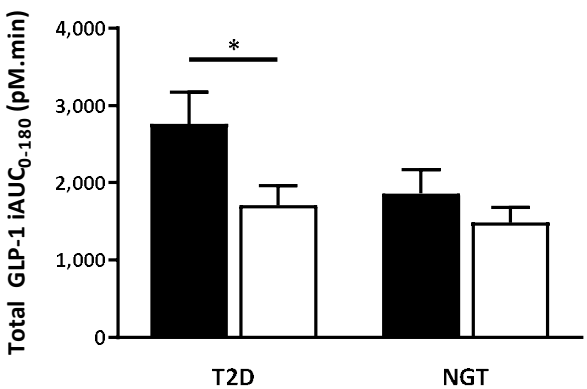
Plasma levels of total GLP-1 and total GIP during the 180-minute MMTT

In individuals with type 2 diabetes, the $iAUC_{0\text{-}180}$ of plasma total GLP-1 levels was significantly higher with the premeal PFB than with the postmeal PFB (2,759 ± 413 pM·min vs. 1,712 ± 249 pM·min, $P = 0.0020$) (Fig. 4A and B). There was no difference in the $iAUC_{0\text{-}180}$ of plasma total GIP levels between the premeal and postmeal PFB (45,420 ± 5,018 pg·min/mL vs. 45,010 ± 4,900 pg·min/mL, $P = 0.8210$) (Fig. 4D and E).

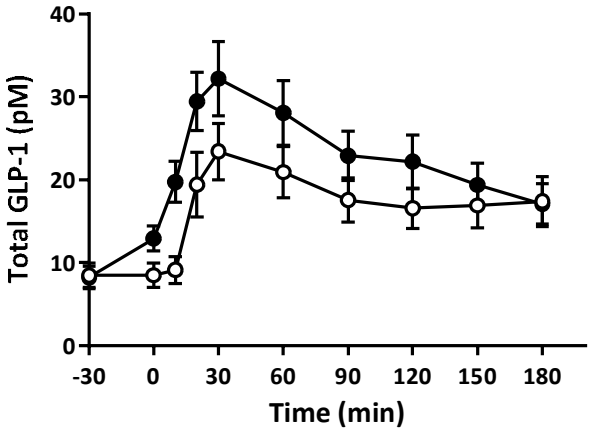
In individuals with NGT, the $iAUC_{0\text{-}180}$ of plasma total GLP-1 (1,860 ± 314 pM·min vs. 1,484 ± 199 pM·min, $P = 0.0857$) (Fig. 4A and C) and total GIP levels (55,380 ± 4,317 pg·min/mL vs. 59,580 ± 5,976 pg·min/mL, $P = 0.1406$) (Fig. 4D and F) were not different between the premeal and postmeal PFB, respectively.

Figure 4. Postprandial levels of total GLP-1 and total GIP during the 180-minute MMTT in individuals with type 2 diabetes and NGT. (A) The $iAUC_{0\text{-}180}$ of plasma total GLP-1 levels. (B) Plasma total GLP-1 levels in type 2 diabetes. (C) Plasma total GLP-1 levels in NGT. (D) The $iAUC_{0\text{-}180}$ of plasma total GIP levels. (E) Plasma total GIP level in type 2 diabetes. (F) Plasma total GIP levels in NGT. Values are presented as mean ± standard error of the mean in the graphs. Black bar/circle, premeal protein-enriched, dietary fiber-fortified bar (PFB); white bar/circle, postmeal PFB. MMTT, mixed meal tolerance test; T2D, type 2 diabetes; NGT, normal glucose tolerance; GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide; $iAUC_{0\text{-}180}$, incremental area under the curve during the 180-minute MMTT. $^{*}P < 0.05$.

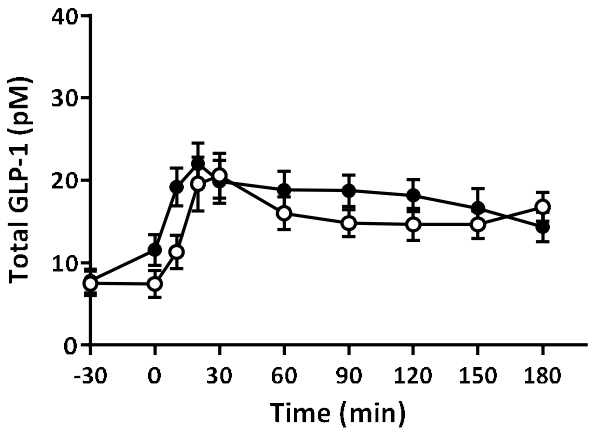
(A)



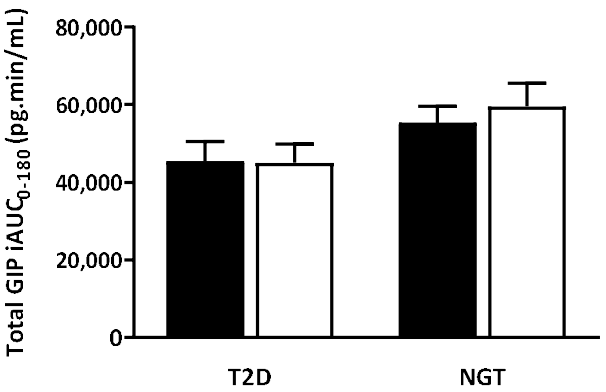
(B)


Total GLP-1 (pM)
40
30
20
10
0
-30
0
30
60
90
120
150
180
Time (min)

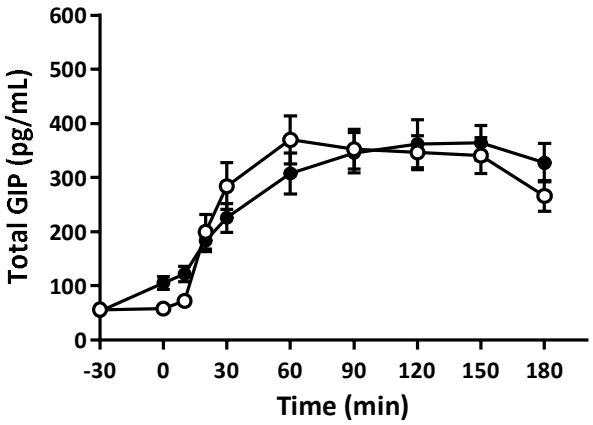
(C)


Total GLP-1 (pM)
40
30
20
10
0
-30
0
30
60
90
120
150
180
Time (min)

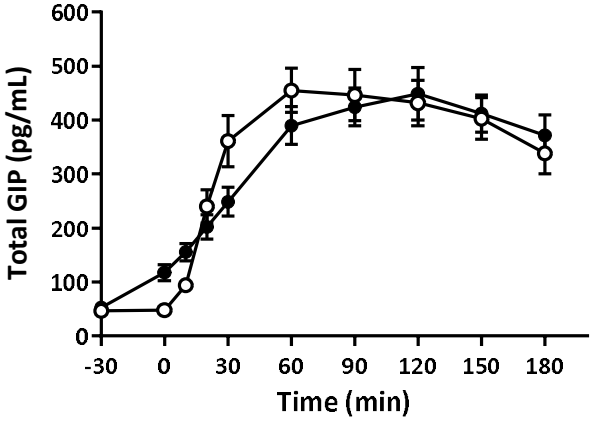
(D)


Total GIP iAUC0-180 (pg.min/mL)
80,000
60,000
40,000
20,000
0
T2D
NGT

(E)


Total GIP (pg/mL)
600
500
400
300
200
100
0
-30
0
30
60
90
120
150
180
Time (min)

(F)


Total GIP (pg/mL)
600
500
400
300
200
100
0
-30
0
30
60
90
120
150
180
Time (min)

Discussion

In the present study, we found that the premeal PFB significantly improved postprandial glucose excursions after a standard test meal compared with the postmeal PFB in individuals with type 2 diabetes and NGT. Previously, a single dose of 50-g whey preload (34) or 4 weeks of 25-g whey preload (33) reduced postprandial hyperglycemia when given before a mixed meal. However, weight gain due to the caloric surplus might be a potential problem of consuming a large amount of protein preload. In a dose-response study, 10 g, 20 g, and 40 g of whey preload reduced the glycemic response by 29%, 47%, and 64%, respectively (41). Accordingly, it is important to determine the minimum effective dose of protein to avoid unintended consequences. To maintain the glucose-lowering effect while reducing the amount of protein, we added 12.7 of dietary fiber to 10.7 g of protein in the form of a cereal bar. We demonstrated that premeal ingestion of PFB improved postprandial glycemic responses in individuals with type 2 diabetes and NGT.

The glucose-lowering effect of premeal PFB was associated with the augmentation of early insulin secretion in individuals with type 2 diabetes, which was indicated by the increase in the IGI and the left shit in the insulin curve during the MMTT. On the contrary, the $iAUC_{0\text{-}180}$ of plasma insulin levels was lower with the premeal PFB than with the postmeal PFB. Early insulin secretion normally suppressed endogenous glucose production after meal ingestion, and the loss of this response contributed to postprandial hyperglycemia in individuals with type 2 diabetes (63-65). These findings denote that early insulin secretion is more important to postprandial glycemic control than total insulin secretion. Additionally,

early insulin secretion in type 2 diabetes was accompanied by enhanced GLP-1 response in the present study. In GLP-1 receptor knockout mice, early insulin response to an oral glucose tolerance test was lower than wild-type mice (66). In individual with type 2 diabetes, decreased early insulin secretion was associated with diminished GLP-1 response during the MMTT (67). A previous study showed that whey preload in individuals with type 2 diabetes reduced postprandial hyperglycemia by increasing both early and late insulin secretion with augmented GLP-1 response during the MMTT compared with placebo (34). In the present study, the increase in late insulin secretion was observed only in the postmeal PFB group, which might be due to the ingestion of PFB. These findings show that early insulin secretion by the premeal PFB was more critical to improving postprandial glycemia than late insulin secretion by the postmeal PFB. However, in individuals with NGT, there was no difference in the IGI between the premeal and postmeal PFB. In addition, postprandial GLP-1 secretion was not different between the premeal and postmeal PFB in individuals with NGT. Thus, the increase in early insulin secretion might result from the exaggerated GLP-1 response in individuals with type 2 diabetes.

In contrast, the premeal PFB might improve postprandial hyperglycemia by its effect on gastric emptying, which was unfortunately not measured in the present study. Gastric emptying accounts for up to 35% of the variance in the initial rise and peak postprandial glucose levels in individuals with type 2 diabetes and NGT (68). Whey protein slowed the gastric emptying rate compared with water or glucose preload (43, 69). Dietary fiber also affected the gastric emptying rate to varying degrees (70-73). Increased viscosity of gastric contents as a result of dietary fiber decreased pyloric flow by reducing the separation of solids from

liquids (74). In general, a high dose of fiber more than 7 g tended to delay gastric emptying, whereas a low dose of fiber had no significant effect (75). Further investigation is required to elucidate the effect of the PFB on gastric emptying in individuals with type 2 diabetes and NGT.

The premeal PFB stimulated postprandial GLP-1 secretion during the MMTT in individuals with type 2 diabetes, but not in those with NGT. This result is inconsistent with previous findings of a reduction in GLP-1 secretion after an oral glucose tolerance test or MMMT in type 2 diabetes compared with in NGT (76, 77). However, GLP-1 secretory response was not different between in individuals with type 2 diabetes and NGT after balancing age, BMI, plasma glucagon levels, and fasting non-esterified fatty acids concentrations (77, 78). In the present study, individuals with type 2 diabetes were older than those with NGT and the BMI was not different between the two groups. Notably, all individuals with type 2 diabetes had been taking metformin until the day before the study. Metformin stimulated GLP-1 secretion by preventing intestinal absorption of bile acids with subsequent activation of the G protein-coupled bile acid receptor 1 (TGR5) and with decreased activation of the farnesoid X receptor in enteroendocrine L cells (79-82). In addition, metformin altered the composition of gut microbiota (82), reduced the lipotoxicity of L cells (83), stimulated the parasympathetic nervous system (84), increased GLP-1 sensitivity of pancreatic beta-cells (85), and might prolong the half-life of active GLP-1 (86). Therefore, it is conceivable that the use of metformin might affect the effect of premeal PFB on GLP-1 secretion, which needs to be addressed in further studies.

The premeal PFB had no effect on postprandial GIP secretion in both individuals with type 2 diabetes and NGT. A meta-analysis showed that there was

no difference in GIP secretion between individuals with type 2 diabetes and NGT (87). Unlike GLP-1 secretion, metformin did not affect GIP secretion, both in rodents and humans (88, 89). As GIP stimulated glucagon secretion and might promote fat accumulation (90), the neutral effect of premeal PFB on GIP secretion might be beneficial.

The present study had some limitations. First. We only evaluated the effect of single administration of the premeal PFB on postprandial glucose excursions in individuals with type 2 diabetes and NGT. Long-term studies are required to ascertain the improvement in a HbA1c or the management of diabetes mellitus. Second, we did not perform a dose-response study with various doses of protein and dietary fiber. Third, we did not evaluate the effect of protein, dietary fiber, and additives separately on postprandial glycemic and hormonal responses. In the present study, 7.7 g of indigestible maltodextrin was used as dietary fiber or prebiotics with acacia gum. In individuals with type 2 diabetes or overweight, long-term treatment of 10 to 34 g of indigestible maltodextrin significantly improved glycemic control (91), insulin resistance (91, 92), and systemic inflammation (92) compared with digestible maltodextrin. Gut microbiota and gut hormones might contribute to the beneficial effects (93, 94). We used stevia and D-sorbitol as a non-nutritive and low-energy sweeteners, respectively, in the PFB. Currently, the metabolic effects of non-nutritive or low-energy sweeteners are unclear in humans (95). Meta-analyses showed that non-nutritive sweeteners might have favorable effects on blood glucose levels (96), which were varied by age, BMI, and diabetic status (97). Additional studies are needed to elucidate the role of each component of PFB. Finally, we do not evaluate the effect of PFB on the gastric emptying rate, appetite, and food intake, which involve in the regulation of postprandial glycemia.

In conclusion, acute administration of premeal PFB significantly improved postprandial glucose excursions in individuals with type 2 diabetes and NGT. Although a more detailed mechanism of action and long-term effect need to be investigated, the PFB could be a nonpharmacological way to manage postprandial glycemia.

Chapter 2.

Effect of premeal consumption of protein-enriched, dietary fiber-fortified bar on the total energy intake in healthy individuals

Introduction

Overweight and obesity are major risk factors for noncommunicable diseases, including diabetes mellitus and cardiovascular disease (98), and associated with loss of disease-free years (99). Intensive weight control with nutrition therapy can prevent or delay the progression to type 2 diabetes and improve its management in individuals with prediabetes or at risk (7, 100, 101).

Diets with a relatively high proportion of protein reduced the risk of a positive energy balance and developing overweight or obesity (102). Increasing the protein content of the diet to 20%–30% of energy decreased food intake under *ad libitum* conditions, resulting in immediate weight loss (102). Sustained high-protein diets could promote weight maintenance through the influence on body composition and energy expenditure (103). In line with these findings, protein preload also had favorable effects on weight management. A whey protein preload reduced appetite and increased satiety by affecting GLP-1, GIP, and other gut hormones, including PYY, cholecystokinin, and ghrelin (104, 105). Moreover, whey protein promoted thermogenesis by increasing protein synthesis (106) through bioactive peptides and branched-chain amino acids (107, 108), which might lead to weight loss. Therefore, protein preload could be a nutritional strategy for weight management.

Previously, we developed a PFB to obtain metabolic benefits of protein and dietary fiber while reducing the caloric surplus by a large amount of protein (60). We demonstrated postprandial glucose-lowering effects of PFB in individuals with type 2 diabetes and NGT (60). In the present study (109), we investigate the effect of PFB on food intake, appetite, and the secretion of gut hormones in healthy individuals.

Methods

Study participants

We recruited 20 healthy individuals in the present study. Eligible participants were individuals aged 19 to 80 years with a BMI of 18.5 to 35.0 kg/m^2, no prior diagnosis of diabetes mellitus, fasting plasma glucose levels < 100 mg/dL, and a HbA1c level < 6.0% according to the National Institute for Health and Care Excellence Guidance for Type 2 Diabetes Mellitus (61). Individuals with an allergy to flour, nuts, legumes, and milk; a previous history of gastrointestinal surgery except for appendectomy, hernia repair surgery, and hemorrhoidectomy; and any chronic illness requiring continuous medications were excluded.

Ethical statement

The study protocol was approved by the institutional review board of Seoul National University Hospital (IRB No. 1705-091-855) and registered at ClinicalTrial.gov (ClinicalTrails.gov Identifier: NCT03431233). All participants provided written informed consent.

Study design and procedures

The present study was a randomized, open-label, crossover, and exploratory study. We investigated the effects of premeal consumption of PFB, usual cereal bar (UB), and water alone (control) on the total energy intake. Eligible participants visited the Clinical Trial Center of Seoul National University Hospital at 08:30 hour after 12 hours of overnight fast on 3 separate days at least 1 week apart. An

intravenous catheter was placed on their nondominant arm for blood sampling. At baseline, blood samples were collected, and appetite and fullness were measured by visual analog scales. The PFB, UB, or water alone (180 mL of still water) were provided to the participants at −15 minutes (08:45 hour). After 15 minutes, the participants ate an *ad libitum* test meal. The amount of the test meal was measured before and after the test meal. Blood sample collection and assessment of appetite and fullness were performed at 0 minutes and every 30 minutes until 120 minutes during the test meal. Serum and plasma were separately immediately by centrifugation and stored at −70℃ for further analyses. All three types of preloads, including the PFB, UB, and water preloads, were provided in a total of 3 visits in a randomized order.

Premeal bar and test meal

The PFB and the UB were made by Ssial Food Inc. (Jecheon, Chungcheongbuk-do, Korea). One serving of PFB (30 g) had 73 kcal and contained 0.4 g of carbohydrates, 9.3 g of whey protein, 1.4 g of soy protein, 0.3 g of fat, and 12.7 g of dietary fiber (60). The ingredients of the PFB were whey protein (36.7%), soy protein nuggets (5.4%), acacia gum (24.6%), indigestible maltodextrin (25.8%), D-sorbitol (6.4%), stevia (0.6%), glycerin fatty acid esters (0.4%), citric acid (0.1%), and vanilla extract (0.1%) (60). The UB had the same calories as the PFB (73 kcal) and contained 13.9 g of carbohydrates, 0.9 g of soy protein, and 1.8 g of fat. The UB was not fortified with protein or dietary fiber.

We provided gimbap as the test meal. Gimbap is a Korean dish made from cooked rice and other ingredients, including vegetables and meat, that are wrapped

with gim (also known as nori) or dried sheets of laver seaweed. A gimbap was sliced into bite-sized pieces. The test meal had 161.1 kcal per 100 grams and contained carbohydrates (81.3% of total dry weight [TDW]), protein (10.6% of TDW), and fat (8.1% of TDW). All test meals were prepared with a standardized recipe.

Measurements

The total amount of the test meal was measured by weighing it before and after an *ad libitum* ingestion in grams. Appetite and fullness were measured by visual analog scales ranged from 0 to 10 scores. Plasma glucose concentrations were measured by the glucose oxidase method (YSI 2300 STAT PLUS analyzer; YSI Inc., Yellow Springs, OH, USA). Plasma concentrations of insulin, GLP-1, PYY, and active ghrelin were measured by a magnetic bead panel (HMHEMAG-34K-04; Merck Millipore, Darmstadt, Germany). All assays were performed according to the manufacturer's instructions.

Study endpoints

The primary endpoint was the total energy intake, including the calories of the premeal supplements. The secondary endpoints were the amount of total calorie intake at 30 minutes (from −15 to 30 minutes), amount of test meal intake (from 0 to 30 minutes and from 30 to 120 minutes), changes in appetite and fullness, and changes in plasma levels of glucose, insulin, GLP-1, PYY, and active ghrelin.

Statistical analysis

Baseline characteristics were presented as mean ± standard deviation for continuous variables and the number or proportions for categorical variables. The results were presented as mean ± standard deviation in tables and mean ± standard error of the mean in graphs. The caloric intake was analyzed by repeated measures ANOVA with Tukey's *post hoc* test. Plasma levels of insulin, GLP-1, PYY, and active ghrelin were analyzed by two-way ANOVA as for time and premeal supplement matched by repeated measures with Tukey's *post hoc* test. The Pearson correlation coefficient was calculated for the correlation between two continuous variables. The iAUC was calculated using the trapezoid rule. Area under the curve (AUC), the sum of iAUC and decremental AUC, was calculated for plasma active ghrelin levels. IGI was calculated as (insulin at 30 minutes – insulin at 0 minutes)/(glucose 30 at minutes – glucose at 0 minutes). All data were analyzed by GraphPad Prism 7 (GraphPad Software Inc., San Diego, CA, USA). P values < 0.05 were accepted as statistically significant.

Results

Characteristics of study participants

A total of 20 healthy individuals were completed the present study. The mean age was 31.4 ± 8.6 years. The BMI was 23.6 ± 3.9 kg/m^2 and HbA1c was 5.2 ± 0.3%. Baseline characteristics of the participants are summarized in Table 3.

Energy intake

The total energy intake, including the calories of PFB or UB, was significantly lower with the PFB preload than with the water preload (904.4 ± 534.9 kcal vs. 1,075.0 ± 508.0 kcal, $P = 0.016$) (Table 4 and Fig. 5A). Compared with the UB preload, the PFB preload reduced the total energy intake with no statistical significance ($P = 0.078$). The meal energy intake, excluding the calories of PFB or UB, was significantly decreased after the PFB and UB preloads compared after the water preload, with a tendency toward a greater reduction after the PFB preload than after the UB preload (Table 4). During the first 30 minutes, the test meal intake was significantly lower with the PFB preload than with the UB preload (Table 4, Fig. 5B). The test meal intake from 30 to 120 minutes was significantly lower with the PFB preload than with the water preload, but there was no difference between the PFB and UB preloads.

Table 3. Baseline characteristic of the study participants

	Healthy individuals (n = 20)
Age, year	31.4 ± 8.6
Sex, n (%) of men	14 (70)
Height, cm	168.9 ± 8.8
Weight, kg	75.4 ± 12.2
BMI, kg/m^2	23.6 ± 3.9
Systolic BP, mmHg	112 ± 12
Diastolic BP, mmHg	75 ± 10
Fasting plasma glucose, mmol/L	4.92 ± 0.55
HbA1c, %	5.2 ± 0.3
Total cholesterol, mmol/L	4.84 ± 0.95
Triglycerides, mmol/L	0.94 ± 0.46
HDL cholesterol, mmol/L	1.54 ± 0.43
LDL cholesterol, mmol/L	2.99 ± 1.04
Creatinine, μmol/L	79.6 ± 17.7
eGFR, mg/min/1.73 m^2	98.2 ± 18.3
AST, IU/L	18 ± 7
ALT, IU/L	20 ± 12

Values are presented as mean ± standard deviation and the number or proportions of the participants. BMI, body mass index; BP, blood pressure; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

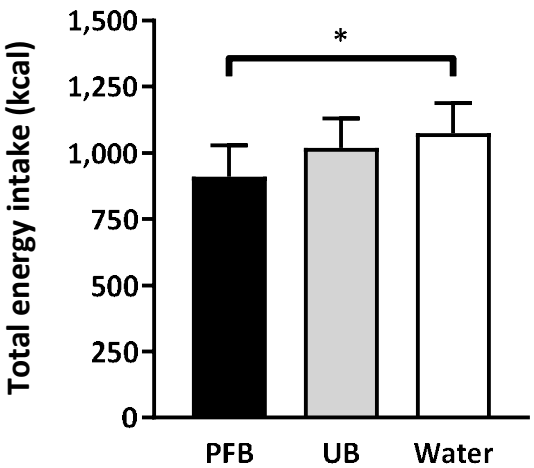
Table 4. Energy intake in healthy individuals with the PFB, UB, and water preloads after the *ad libitum* test meal

Energy intake	Preload			*P* value			
	PFB	UB	Water	ANOVA	PFB vs. Water[a]	UB vs. Water[a]	PFB vs. UB[a]
Total energy intake 0–120 min, kcal	904.4 ± 534.9	1,013.1 ± 499.3	1,075.0 ± 508.0	0.008	0.016	0.471	0.078
Total meal intake 0–120 min, kcal	831.4 ± 534.9	940.1 ± 499.3	1,075.0 ± 508.0	< 0.001	0.041	0.198	0.041
Total energy intake 0–30 min, kcal	666.5 ± 327.5	738.5 ± 294.3	713.5 ± 219.1	0.161	NA	NA	NA
Total meal intake 0–30 min, kcal	593.5 ± 327.5	665.5 ± 294.3	713.5 ± 219.1	< 0.001	0.001	0.044	0.078
Water intake, mL	544.0 ± 237.9	541.5 ± 273.5	526.0 ± 190.2	0.922	NA	NA	NA

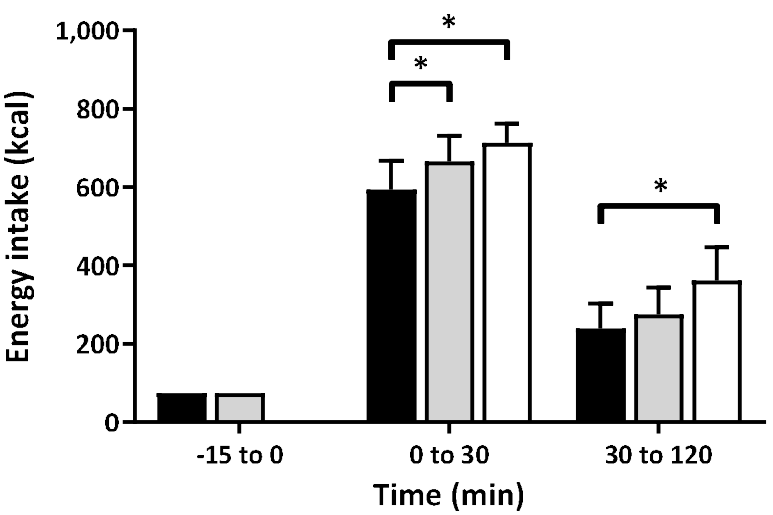
Values are presented as mean ± standard deviation. PFB, protein-enriched, dietary fiber-fortified bar; UB, usual cereal bar; ANOVA, analysis of variance; NA, not applicable. [a]*P* values were calculated by Tukey's *post hoc* analysis when the *P* for ANOVA was < 0.05.

Figure 5. Effect of the PFB, UB, and water preloads on the total energy intake after the *ad libitum* test meal in healthy individuals. (A) Total energy intake for 120 minutes. (B) Total energy intake according to each time interval. Values are presented as mean ± standard error of the mean in the graphs. Black bar, PFB; Gray bar, UB; White bar, water. PFB, protein-enriched, dietary fiber-fortified bar; UB, usual cereal bar. $^{*}P < 0.05$ by *post hoc* analyses.

(A)



(B)



Appetite and fullness

Appetite and fullness after the preloads are depicted in Fig. 6A and B. Baseline appetite and fullness were not different between the three preloads. Immediately after the intake of the PFB and UB preloads (at 0 minutes), appetite tended to decrease and fullness tended to increase. There was a significant time-by-preload interaction for fullness ($P = 0.011$) but not for appetite ($P = 0.469$). In a *post hoc* analysis of each time point, the PFB preload significantly increased fullness at 0 minutes, when individuals started eating the test meal, compared with the water preload ($P = 0.006$).

Plasma levels of glucose, insulin, and gut hormones

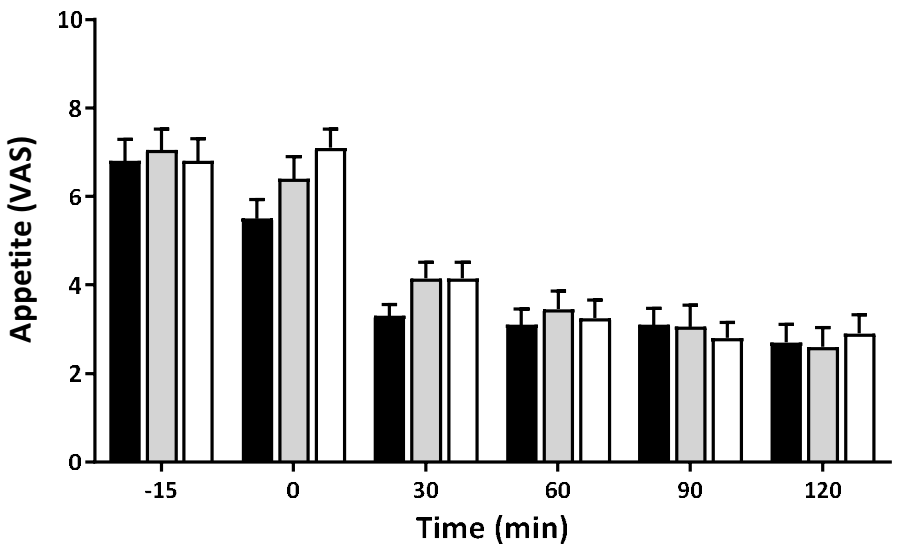
Postprandial glucose levels were significantly lower with the PFB preload than with the UB and water preloads at 30 and 60 minutes after the test meal (Fig. 7A). There was a significant time-by-preload interaction for plasma glucose levels ($P < 0.001$) (Fig. 7B). However, there was no significant difference in plasma insulin levels between the three preloads, although the PFB preload tended to be higher at 30 minutes and lower at 120 minutes (Fig. 7C and D). The IGI was significantly increased with the PFB preload compared with the UB or water preloads (Fig. 7E)

Plasma GLP-1 levels were significantly higher with the PFB preload than with the UB and water preloads at 30 minutes after the test meal (Fig. 8A). There was a significant time-by-preload interaction for plasma GLP-1 levels ($P < 0.001$) (Fig. 8A). In addition, the iAUC of plasma GLP-1 levels was significantly higher with the PFB preload than with the UB (6,173.6 ± 3,834.2 pg·min/mL vs. 2,731.6 ±

2,620.1 pg·min/mL, $P < 0.001$) and water preloads (6,173.6 ± 3,834.2 pg·min/mL vs. 3,086.0 ± 2,433.0 pg·min/mL, $P < 0.001$) (Fig. 8B). Plasma PYY levels started to increase after the intake of the PFB and UB preloads, which were further augmented after the ingestion of the test meal. However, there was no significant difference between the three preloads (Fig. 8C). The iAUC of plasma PYY levels only showed a higher tendency with the PFB and UB preloads than with the water preload (Fig. 8D). Plasma active ghrelin levels were initially decreased after the test meal, but no significant difference was found between the three preloads (Fig. 8E). The iAUC of plasma PYY levels tended to be higher with the PFB preload than with the UB or water preloads (Fig. 8F).

Figure 6. Effect of the PFB, UB, and water preloads on appetite and fullness after the *ad libitum* test meal in healthy individuals. (A) Changes in appetite. (B) Changes in fullness. Values are presented as mean ± standard error of the mean in the graphs. For changes in appetite, the *P* for time, preloads, and time-by-preload were < 0.001, 0.560, and 0.469, respectively. For changes in fullness, the *P* for time, preloads, and time-by-preload were < 0.001, 0.880, and 0.011, respectively. Black bar, PFB; Gray bar, UB; White bar, water. PFB, protein-enriched, dietary fiber-fortified bar; UB, usual cereal bar; VAS, visual analog scales. $^{*}P < 0.05$ by *post hoc* analyses.

(A)



(B)

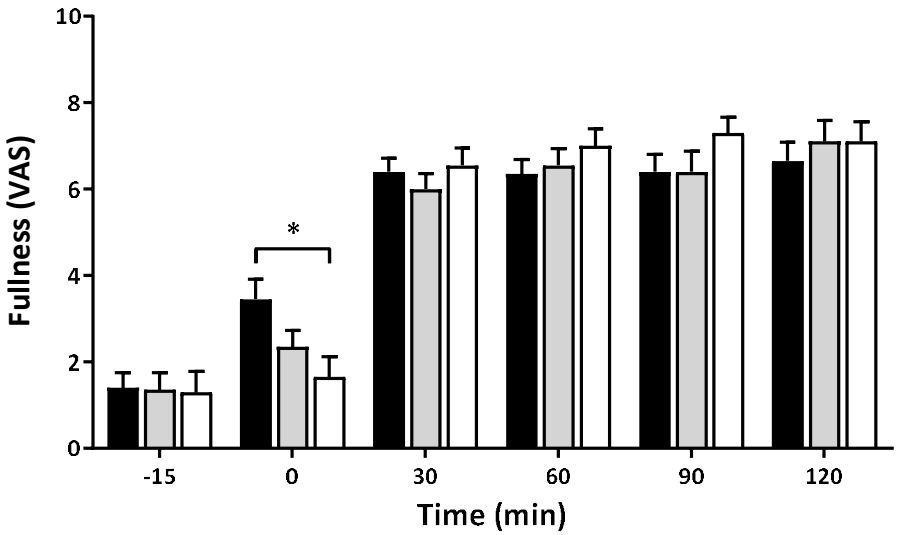
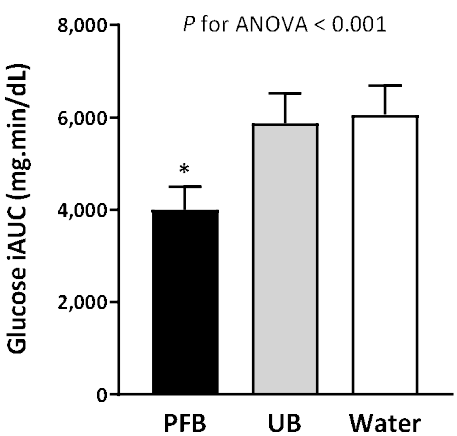
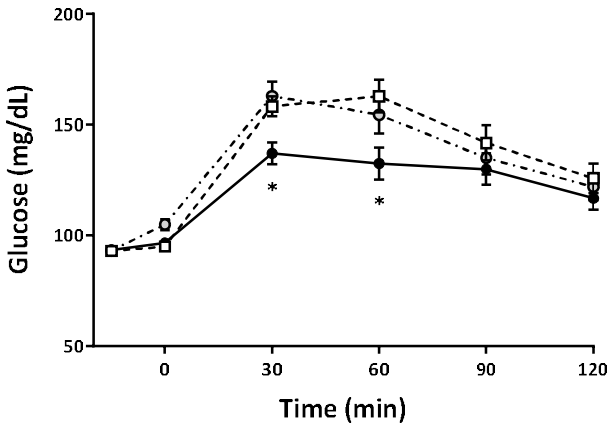


Figure 7. Plasma levels of glucose and insulin with the PFB, UB, water preloads after the *ad libitum* test meal in healthy individuals. (A) The iAUC of plasma glucose levels. (B) Changes in plasma glucose levels. (C) The iAUC of plasma insulin levels. (D) Change in plasma insulin levels. (E) Insulinogenic index. Values are presented as mean ± standard error of the mean in the graphs. For changes in plasma glucose levels, the *P* for time, preloads, and time-by-preload interaction were < 0.001, 0.102, and < 0.001, respectively. For changes in plasma insulin levels, the *P* for time, preloads, and time-by-preload interaction were < 0.001, 0.096, and < 0.001, respectively. Black bar/circle, PFB; Gray bar/circle, UB; White bar/square, water. PFB, protein-enriched, dietary fiber-fortified bar; UB, usual cereal bar; iAUC, incremental area under the curve. $^{*}P < 0.05$ by *post hoc* analyses for the PFB preload vs. both UB and water preloads.

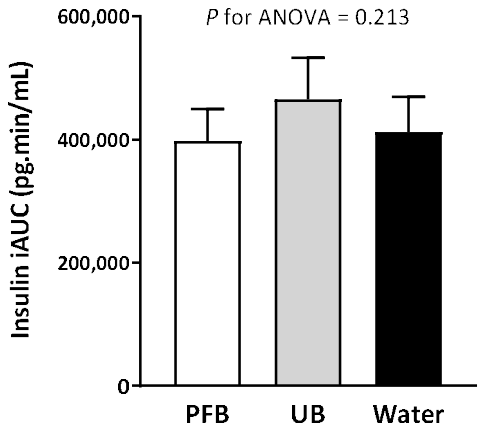
(A)



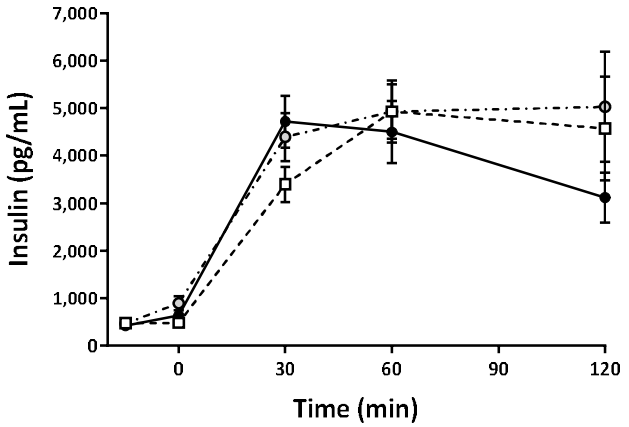
(B)


Glucose (mg/dL)
200
150
100
50
0
30
60
90
120
Time (min)
*
*

(C)


P for ANOVA = 0.213
Insulin iAUC (pg.min/mL)
600,000
400,000
200,000
0
PFB
UB
Water

(D)


Insulin (pg/mL)
7,000
6,000
5,000
4,000
3,000
2,000
1,000
0
0
30
60
90
120
Time (min)

(E)

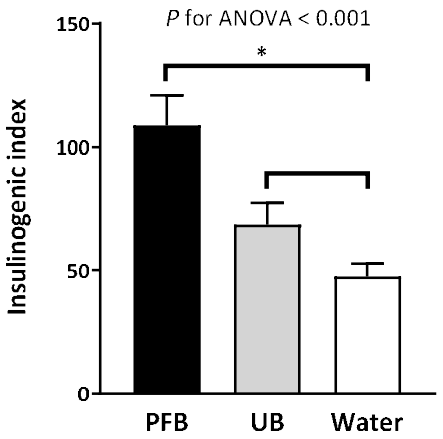
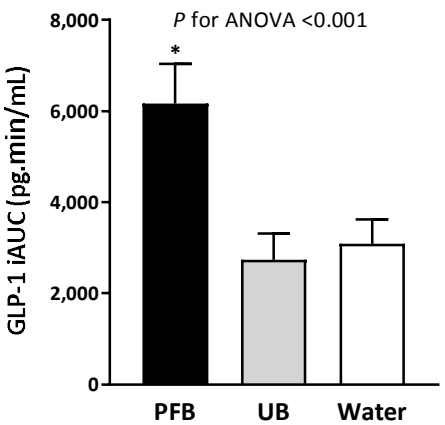
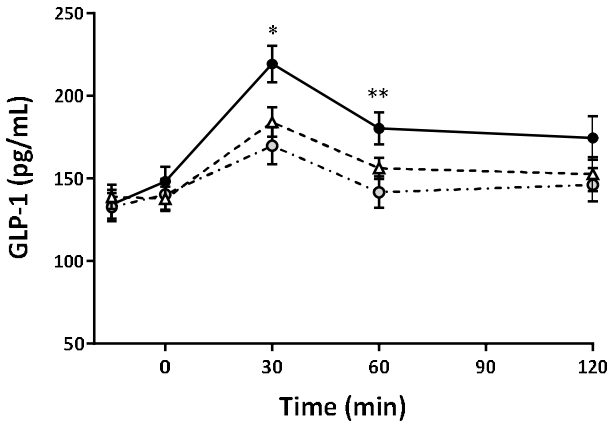

P for ANOVA < 0.001
*
150
100
50
0
Insulinogenic index
PFB
UB
Water

Figure 8. Plasma levels of GLP-1, PYY, and active ghrelin with the PFB, UB, water preloads after the *ad libitum* test meal in healthy individuals. (A) The iAUC of plasma GLP-1 levels. (B) Changes in plasma GLP-1 levels. (C) The iAUC of plasma PYY levels. (D) Change in plasma PYY levels. (E) The AUC of plasma active ghrelin levels. (F) Changes in plasma active ghrelin levels. Values are presented as mean ± standard error of the mean in the graphs. For changes in plasma GLP-1 levels, the *P* for time, preloads, and time-by-preload interaction were < 0.001, 0.096, and < 0.001, respectively. For changes in plasma PYY levels, the *P* for time, preloads, and time-by-preload interaction were < 0.001, 0.972, and 0.638, respectively. For changes in plasma active ghrelin levels, the *P* for time, preloads, and time-by-preload interaction were 0.017, 0.710, and 0.912, respectively. Black bar/circle, PFB; Gray bar/circle, UB; White bar/square, water. GLP-1, glucagon-like peptide-1; PYY, peptide-YY; PFB, protein-enriched, dietary fiber-fortified bar; UB, usual cereal bar; iAUC, incremental area under the curve; AUC, area under the curve. $^{*}P < 0.05$ and $^{**}P < 0.05$ were by *post hoc* analyses for the PFB vs. both UB and water and for the PFB vs. the water preloads, respectively.

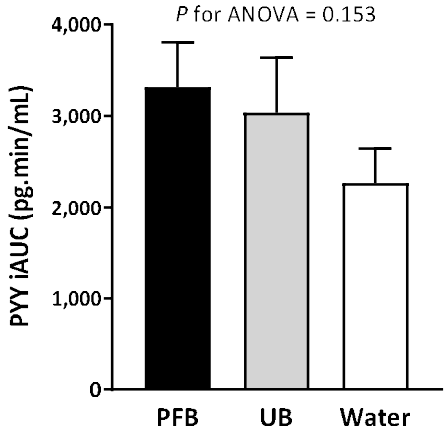
(A)



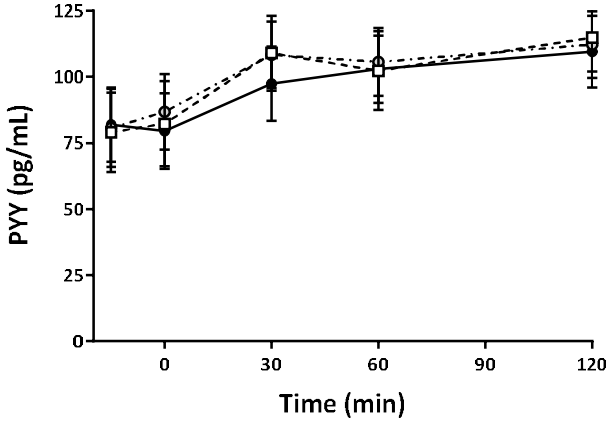
(B)


250
200
150
100
50
GLP-1 (pg/mL)
*
**
0
30
60
90
120
Time (min)

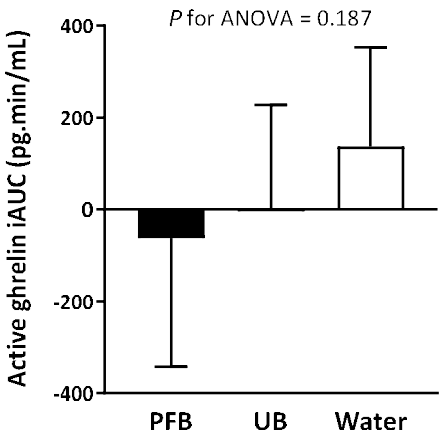
(C)


P for ANOVA = 0.153
4,000
3,000
2,000
1,000
0
PYY iAUC (pg.min/mL)
PFB
UB
Water

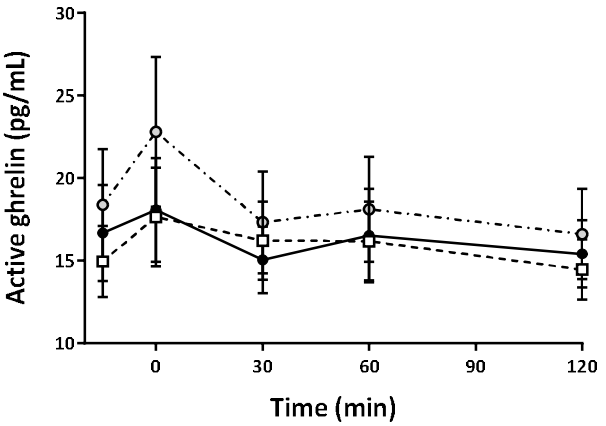
(D)


125
100
75
50
25
0
PYY (pg/mL)
0
30
60
90
120
Time (min)

(E)


P for ANOVA = 0.187
Active ghrelin iAUC (pg.min/mL)
400
200
0
-200
-400
PFB
UB
Water

(F)


Active ghrelin (pg/mL)
30
25
20
15
10
0
30
60
90
120
Time (min)

Correlation between energy intake and plasma levels of insulin and gut hormones

Correlation analyses were performed to evaluate that which hormonal factors were responsible for the decrease in the energy intake with the PFB preload compared with the water preload. At each time point, the differences in energy intake and plasma levels of insulin and gut hormones between the PFB and water preloads were calculated for correlation analyses. Interestingly, the difference in plasma PYY levels between the two preloads at −15, 0, and 30 minutes and the difference in the AUC of plasma PYY levels between the two preloads showed a significant negative correlation with the difference in the energy intake between the two preloads for the first 30 minutes (all $P < 0.05$) (Table 5). The difference in plasma PYY levels between the two preloads at 30 minutes showed the highest negative correlation with the difference in the energy intake between the two preloads for the first 30 minutes ($r = -0.541$, $P = 0.014$) (Table 5, Fig. 9F).

Table 5. Correlation analyses of the differences in the energy intake and hormonal changes between the PFB and water preloads at each time point

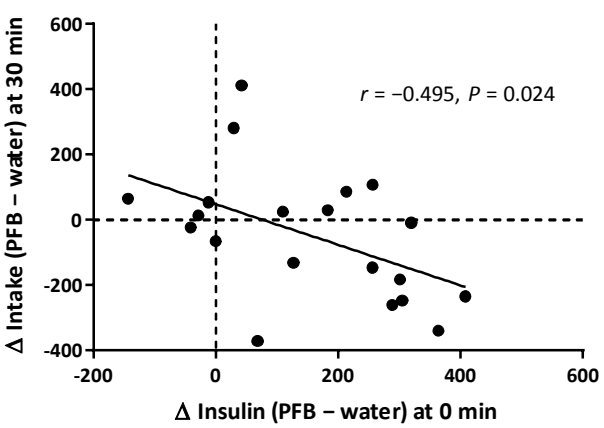
	Δ Energy intake at 30 min	Δ Energy intake at 120 min
Δ Insulin at −15 min	0.367 (0.11)	0.259 (0.27)
Δ Insulin at 0 min	−0.495 (0.03)*	−0.357 (0.12)
Δ Insulin at 30 min	0.252 (0.28)	0.482 (0.03)*
Δ Insulin at 60 min	0.179 (0.45)	0.441 (0.05)*
Δ Insulin at 120 min	−0.034 (0.89)	0.093 (0.70)
Δ Insulin AUC	0.138 (0.56)	0.399 (0.08)
Δ Insulin iAUC	0.113 (0.64)	0.386 (0.09)
Δ GLP-1 at −15 min	−0.041 (0.86)	0.291 (0.21)
Δ GLP-1 at 0 min	−0.117 (0.62)	0.181 (0.45)
Δ GLP-1 at 30 min	0.277 (0.24)	0.199 (0.40)
Δ GLP-1 at 60 min	0.221 (0.35)	0.398 (0.08)
Δ GLP-1 at 120 min	0.285 (0.22)	0.521 (0.02)*
Δ GLP-1 AUC	0.234 (0.32)	0.420 (0.07)
Δ GLP-1 iAUC	0.395 (0.08)	0.189 (0.43)
Δ PYY at −15 min	−0.513 (0.02)*	−0.284 (0.22)
Δ PYY at 0 min	−0.501 (0.02)*	−0.199 (0.40)
Δ PYY at 30 min	−0.541 (0.01)*	−0.071 (0.77)
Δ PYY at 60 min	−0.279 (0.23)	0.056 (0.81)
Δ PYY at 120 min	−0.341 (0.14)	0.07 (0.98)
Δ PYY AUC	−0.451 (0.05)*	−0.042 (0.86)
Δ PYY iAUC	−0.085 (0.72)	0.217 (0.36)
Δ Ghrelin at −15 min	0.104 (0.66)	0.294 (0.21)

	Δ Energy intake at 30 min	Δ Energy intake at 120 min
Δ Ghrelin at 0 min	0.131 (0.58)	0.139 (0.56)
Δ Ghrelin at 30 min	−0.019 (0.94)	−0.160 (0.50)
Δ Ghrelin at 60 min	0.166 (0.49)	0.323 (0.17)
Δ Ghrelin at 120 min	−0.298 (0.20)	−0.316 (0.18)
Δ Ghrelin AUC	0.100 (0.68)	0.221 (0.35)
Δ Ghrelin iAUC	−0.369 (0.11)	−0.432 (0.06)

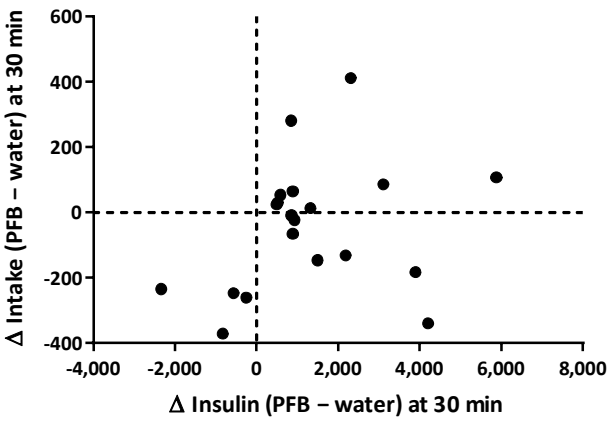
The Pearson correlation efficient was calculated for linear association. *P* values for the linear correlation analyses were presented in parenthesis. PFB, protein-enriched, dietary fiber-fortified bar; GLP-1, glucagon-like peptide-1; PYY, peptide YY; Ghrelin, active ghrelin; AUC, area under the curve; iAUC, incremental area under the curve. $^{*}P < 0.05$.

Figure 9. Correlation analyses of the difference in the energy intake for the first 30 minutes and that in plasma levels of insulin and gut hormones at each time point between the PFB and water preloads. (A) Correlation of the difference in energy intake at 30 minutes and insulin at 0 minutes between the PFB and water preloads. (B) Correlation of the difference in energy intake at 30 minutes and insulin at 30 minute between the PFB and water preloads. (C) Correlation of the difference in energy intake at 30 minutes and GLP-1 at 0 minutes between the PFB and water preloads. (D) Correlation of the difference in energy intake at 30 minutes and GLP-1 at 30 minutes between the PFB and water preloads. (E) Correlation of the difference in energy intake at 30 minutes and PYY at 0 minutes between the PFB and water preloads). (F) Correlation of the difference in energy intake at 30 minutes and PYY at 30 minute between the PFB and water preloads. (G) Correlation of the difference in energy intake at 30 minutes and active ghrelin at 0 minutes between the PFB and water preloads. (H) Correlation of the difference in energy intake at 30 minutes and active ghrelin at 30 minute between the PFB and water preloads. Δ, difference; (PFB – water), between the PFB and water preloads.

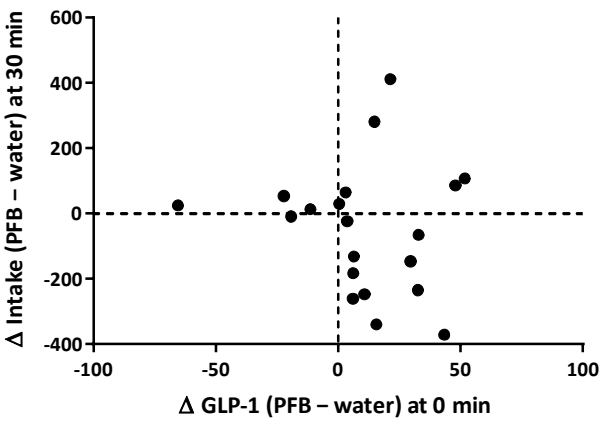
(A)



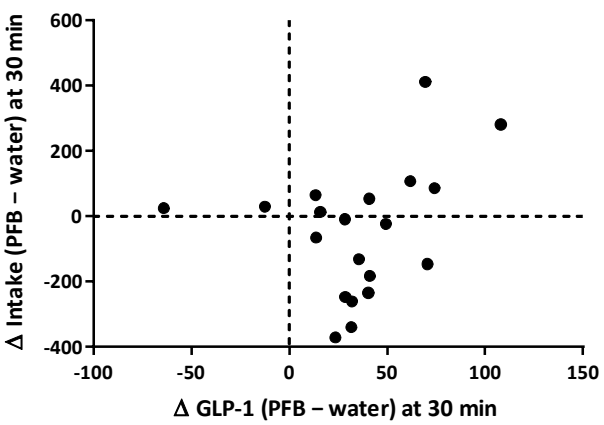
(B)


Δ Intake (PFB – water) at 30 min
600
400
200
0
-200
-400
-4,000
-2,000
0
2,000
4,000
6,000
8,000
Δ Insulin (PFB – water) at 30 min

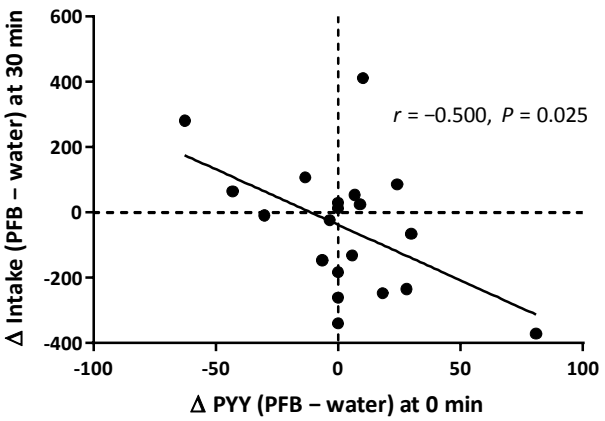
(C)


Δ Intake (PFB – water) at 30 min
600
400
200
0
-200
-400
-100
-50
0
50
100
Δ GLP-1 (PFB – water) at 0 min

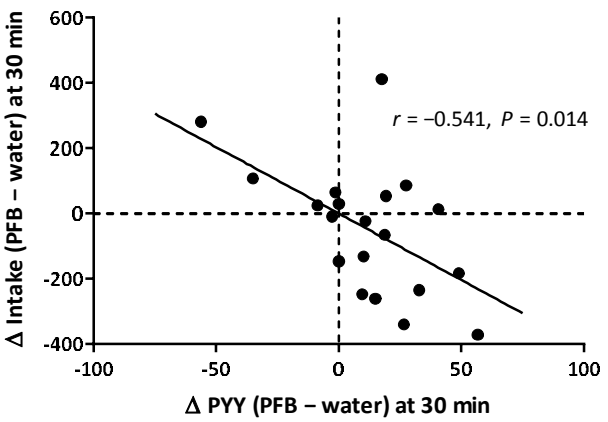
(D)


Δ Intake (PFB – water) at 30 min
600
400
200
0
-200
-400
-100
-50
0
50
100
150
Δ GLP-1 (PFB – water) at 30 min

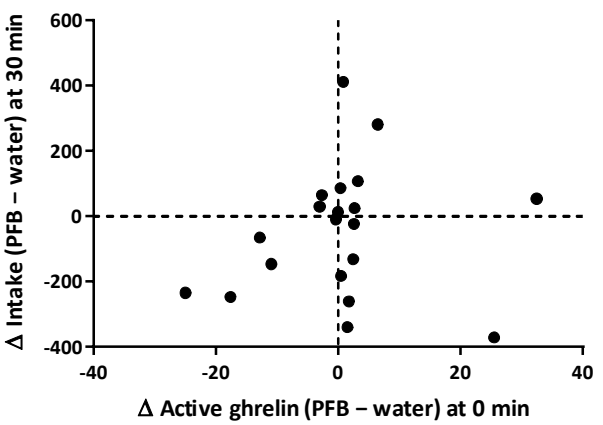
(E)


600
400
200
0
-200
-400
-100
-50
0
50
100
r = −0.500, P = 0.025
Δ Intake (PFB – water) at 30 min
Δ PYY (PFB – water) at 0 min

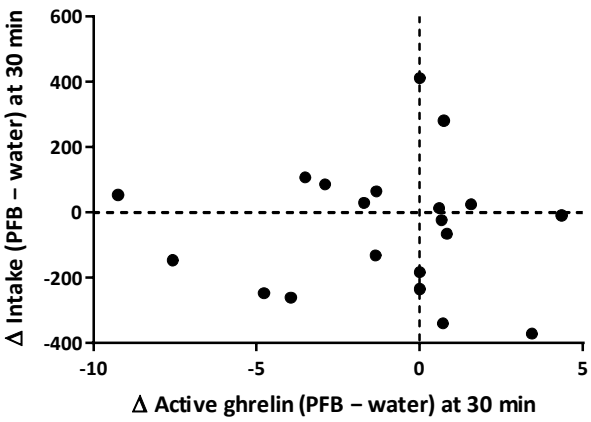
(F)


600
400
200
0
-200
-400
-100
-50
0
50
100
r = −0.541, P = 0.014
Δ Intake (PFB – water) at 30 min
Δ PYY (PFB – water) at 30 min

(G)


600
400
200
0
-200
-400
-40
-20
0
20
40
Δ Intake (PFB – water) at 30 min
Δ Active ghrelin (PFB – water) at 0 min

(H)


600
400
200
0
-200
-400
-10
-5
0
5
Δ Intake (PFB – water) at 30 min
Δ Active ghrelin (PFB – water) at 30 min

Discussion

In the present study, the PFB preload that was fortified with a modest amount of protein and dietary fiber significantly reduced the energy intake of the total energy intake and subsequent test meal compared with the water preload. The UB preload, which was the same calorie as the PFB but mainly composed of carbohydrates, did not reduce the total energy intake. Along with the decrease in the energy intake, the PFB preload decreased plasma glucose levels and increased GLP-1 secretion after the test meal.

Protein preload has been reported to reduce subsequent food intake (110). An acute administration of protein slowed gastric emptying and increased satiety which were associated with its effect on gut hormone secretion, including an increase in GLP-1, PYY, and cholecystokinin and a decrease in ghrelin (102, 105). A 50 g of whey preload reduced the energy intake after a buffet compared with a glucose preload (111). In a previous study, 45 to 50 g of whey or soy protein preloads increased satiety and decreased subsequent food intake compared with egg albumin. These findings indicate that the effect of protein on satiety and food intake may differ depending on types or sources of protein. In long-term studies, supplementation with whey protein (56 g per day) before a meal showed a 1.8 kg of weight reduction for 23 weeks compared with maltodextrin supplementation (112). When offered with a low-calorie diet, a 50 g of whey protein preload reduced body weight by 8.0% for 6 months compared with a maltodextrin preload (−4.1%) (113). However, a large amount of protein required in these studies might offset its effect on weight loss due to the caloric surplus. In a dose-response study, different doses of whey preload reduced subsequent food intake in a dose-

dependent manner, where the reduction of food intake was observed only with 20 g or more of whey protein (41). However, the total energy intake, including whey protein, was not changed even with the highest dose of whey preload (41). Thus, the addition of another supplement to protein might be a reasonable method to enhance the effect of nutrient preload.

In this regard, dietary fiber might be a good supplement to protein because it had the metabolic benefits with a low amount of calories (114). In overweight individuals, 12 weeks of indigestible maltodextrin significantly reduced body weight, body fat percentage, and hunger compared with digestible maltodextrin (91). Evening meal of boiled barley kernel reduced hunger and food intake on the following day compared with white wheat bread (115). The effects of dietary fiber on hunger and satiety showed a dose-response relationship (116). Although it has not yet been fully understood, gastrointestinal motility, gut microbiota, and gut hormones might be involved in the beneficial effects of dietary fiber (93, 94). The physicochemical properties of dietary fiber delayed the gastric emptying rate after a meal (56). Fermentation of dietary fiber by gut microbiota produced short-chain fatty acids (SCFAs), which may exert diverse effects through the activation of cognate receptors (117). SCFAs stimulate the secretion of GLP-1 and PYY in enteroendocrine L cells through G-protein coupled receptor (GPR) 43 *in vitro* (118). Colonic infusion of propionate stimulated the secretion of GLP-1 and PYY, which was attenuated in GPR43 knockout mice (118). SFCAs were also reported to stimulate leptin production in adipocyte and to suppress fat accumulation in the adipose tissue through the action of GPR43 (119, 120). In addition, dietary fiber may modulate gut microbiota by affecting its composition (121, 122). A meta-analysis revealed that the supplementation of soluble dietary fiber for 2 to 17

weeks significantly reduced body weight, decreased fat mass, and lowered fasting glucose and insulin levels compared with placebo (123). The consumption of dietary fiber was associated with lower cardiovascular risk factors, including weight gain, abdominal obesity, blood pressure, plasma insulin levels, and lipid profiles in health individuals (124). In patients with type 2 diabetes, the ingestion of dietary fiber-enriched cereals improved postprandial glucose excursions (125). Accordingly, dietary fiber has the beneficial metabolic effects as nutrient preload in combination with protein.

In the present study, we used a modest dose (10.7 g) of protein including 9.3 g of whey protein and 1.4 g of soy protein. Previous studies provided 20 to 50 g of protein to assess the acute effect of nutrient preload on appetite and food intake (41, 111, 126). A 10 g of whey preload did not reduce the subsequent food intake in healthy individuals (41). In individuals with type 2 diabetes, a 15 g of whey preload improved postprandial glycemia and increased satiety, but did not affect the gut hormone responses (127). In contrast, in the present study, a modest dose of protein preload significantly reduced the subsequent and total energy intake by 23% and 16%, respectively, in combination with 12.7 of dietary fiber. In line with our findings, a beverage preload that contained 17 g of protein and 6 g of dietary fiber significantly reduced hunger and desire to eat and tended to decrease subsequent food intake compared with placebo that contained 1 g of protein and 3 g of fiber in individuals with overweight or obesity (128). Consequently, premeal consumption of protein and dietary fiber may have an additive or synergistic effect on satiety, food intake, and GLP-1 secretion.

The PFB preload affected the secretion of gut hormone after the test meal. Postprandial GLP-1 secretion was prominently increased with the PFB preload

compared with the UB or water preloads. However, the difference in GLP-1 responses did not correlate with that in the energy intake between the PFB and water preloads. Intriguingly, the difference in plasma PYY levels between the PFB and water preloads showed a negative correlation with that in the energy intake, which indicates that increased PYY secretion might contribute to the reduction in food intake. Furthermore, PYY secretion was tended to increase with the PFB preload than with the water preload. It is well known that PYY, which is secreted by L cells, acts directly on the neuropeptide Y neuron in the arcuate nucleus and exerts an anorectic effect (129). Similarly, the energy intake was negatively correlated with plasma PYY levels but not with GLP-1 levels in elderly individuals with a whey preload after an *ad libitum* food intake (130). These results suggest that PYY might have a role as a regulator for the energy intake after premeal consumption of whey protein.

The IGI was higher with the PFB preload than with the UB or water preloads. Given the plasma glucose increment, this finding indicates that insulin secretion is relatively higher with the PFB preload than the other two preloads. Augmented postprandial secretion of GLP-1 could contribute to the increase in insulin secretion, which was possibly induced by protein and dietary fiber in the PFB. The ingestion of protein directly stimulated L cells to secrete GLP-1 (131, 132). As formerly mentioned, SCFAs, produced by the fermentation of dietary fiber, are also able to stimulate the secretion of GLP-1 (118). We previously reported that the PFB preload enhanced early insulin secretion with augmented GLP-1 response in individuals with type 2 diabetes (60). These findings reveal that the protein and dietary fiber in the PFB contributed to an increase in postprandial insulin secretion.

The present study has some limitations. First, the PFB had other ingredients

besides protein and dietary fiber. These ingredients could have any metabolic effects. In intervention studies, non-nutritive sweeteners significantly reduced weight gain in normal weight, overweight, and obese adolescents (133, 134). On the contrary, observational studies have reported that non-nutritive or low-energy sweeteners are associated with the risk of weight gain and detrimental conditions, including type 2 diabetes and cardiovascular disease (95). Artificial sweeteners induced glucose intolerance by changing the gut microbiota in mice and humans (135). However, meta-analysis showed that non-nutritive sweeteners can be used safely in humans (96). More convincing evidence is needed to clarify their effects on health outcomes. Second, we used gimbap as the test meal. Although gimbap is a very popular food for Koreans, meals with different compositions might lead to different results. Third, we did not measure the gastric emptying rate, which can be affected by whey protein and dietary fiber.

In conclusion, acute administration of PFB that contained a modest amount of protein and dietary fiber decreased the energy intake, lowered postprandial glucose levels, and enhanced GLP-1 secretion in health individuals. Further investigation is required to confirm the long-term effects of PFB on overweight and obesity.

Summary and Conclusions

Premeal consumption of PFB that contained a modest amount of protein and dietary fiber improved postprandial glucose excursions in individuals with type 2 diabetes and normal glucose tolerance and reduced postprandial glucose levels, appetite, and food intake in healthy individuals with the changes in gut hormones, including augmented GLP-1 secretion. The PFB preload might be a feasible nutritional strategy in the management of diabetes mellitus and obesity. Further investigation is required to determine its long-term effect and safety.

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국문초록

식전 부하의 내당능, 식욕 및 음식 섭취에 대한 효과 연구

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당뇨병과 비만은 대표적인 비감염성 질환으로 전세계적으로 이로 인한 질병부담이 크게 증가하고 있어 이에 대한 효과적인 예방과 치료가 필요하다. 영양요법은 당뇨병과 비만 관리에서 가장 중요한 부분으로 적절하게 수행될 경우 당뇨병과 비만의 발생 위험을 낮추고 치료 효과를 높여 질병의 예후를 개선할 수 있다. 당뇨병과 비만 환자의 식사요법은 기본적으로 적절한 양의 질 좋은 식사를 섭취하는 것이다. 하지만 최근 음식의 양이나 질에 더해 음식을 섭취하는 시기나 순서가 식사요법에 중요하다는 연구 결과들이 보고되고 있다. 이를 이용한 영양요법은 기존의 식습관을 크게 바꾸지 않으면서 혈당과 체중 조절에 이로운 효과를 기대할 수 있어 향후 효과적인 치료 전략이 될 수 있다.

식전 부하란 식사 전 정해진 시간에 소량의 음식이나 영양소를 섭취하는 것을 말한다. 식전 부하의 대사적인 효과는 주로 우유 단백의 일종인 유청 단백에서 보고되었는데 당뇨병 환자를 포함한 다양한 대상군에서 식후 혈당을 낮추고 음식 섭취량을 감소시켰다. 하지만 이 방법이 임상적으로 유의한 효과를 보이기 위해서는 하루 50 g 정도의 단백 섭취가 필요하였다. 이는 약 200 kcal에 해당하는 양으로써 장기간 섭취할 경우 열량 과잉으로 인해 체중 증가 등의 문제가 발생할 수 있다. 이에 본 연구에서는 이러한 단점을 개선하고 식전 부하의 대사 효과는 유지하기 위해 단백질을 10.7 g으로 감량하는 대신 12.7 g의 식이섬유를 첨가한 강화

시리얼바를 개발하여 제2형 당뇨병 환자와 정상인에서 식후 혈당, 식욕 및 음식 섭취에 대한 효과를 평가하였다.

강화시리얼바의 식후 혈당 개선 효과는 제2형 당뇨병 환자와 정상 내당능인 사람 각각 15명(총 30명)을 대상으로 평가하였다. 연구는 무작위 배정 개방 교차연구로 진행되었다. 피험자들은 배정 순서에 따라 30분 전에 강화시리얼바를 섭취한 뒤 시험식을 섭취하거나 시험식을 섭취한 뒤 강화시리얼바를 섭취하도록 하였으며, 혼합식 부하검사를 통해 혈당, 인슐린 및 위장관호르몬의 변화를 측정하였다. 연구 결과 강화시리얼바를 식전에 투여하면 강화시리얼바를 식후에 투여한 경우 비해 제2형 당뇨병 환자(14,723 ± 1,310 mg·min/dL vs. 19,642 ± 1,367 mg·min/dL, P = 0.0002)와 정상 내당능인 사람 (3,943 ± 416 mg·min/dL vs. 4,827 ± 520 mg·min/dL, P = 0.0296) 모두 식후 혈당이 유의하게 감소하였다. 제2형 당뇨병 환자의 경우 식후 혈당 감소와 함께 초기 인슐린 분비와 식후 glucagon-like peptide-1 분비가 유의하게 증가하였다.

강화시리얼바의 식욕 및 음식 섭취량에 대한 효과는 건강 자원자를 대상으로 평가하였다. 연구는 무작위 배정 개방 교차연구로 진행되었으며 총 20명이 연구에 참여하였다. 피험자들은 배정 순서에 따라 식전 부하로 강화시리얼바, 일반 시리얼바 또는 물 중 하나를 섭취한 뒤 15분 후 2시간 동안 시험식을 제한 없이 섭취하도록 하였으며, 식욕, 충만감과 함께 혈당, 인슐린 및 위장관호르몬의 변화를 측정하였다. 연구 결과 강화시리얼바의 식전 섭취는 물을 섭취한 경우에 비해 총 열량 섭취를 유의하게 감소시켰다(904.4 ± 534.9 kcal vs. 1,075.0 ± 508.0 kcal, P = 0.016). 또한 강화시얼바는 일반 시리얼바나 물을 섭취한 경우 비해 충만감을 유의하게 증가시켰으며 식후 혈당을 낮추고 glucagon-like peptide-1 분비를 증가시켰다.

두 연구 모두 위장관불편감을 포함해 강화시리얼바 섭취와 관련된 이상 반응은 발생하지 않았다.

결론적으로 강화시리얼바는 제2형 당뇨병 환자와 정상 내당능인 사람에서 위장관호르몬의 변화와 함께 식후 혈당, 식욕 및 음식 섭취를 감소

시킴으로써 혈당과 열량 섭취 조절에 이로운 효과를 보여주었다.

주요어 : 식욕, 식이섬유, 식후 고혈당, 열량 섭취, 유청 단백, 위장관호르몬

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