JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

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

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Keywords
Dietary fiber, Postprandial hyperglycemia, Whey proteins

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J Diabetes Investig 2018; 9: 1110–1118

doi: 10.1111/jdi.12831

Clinical Trial Registry
ClinicalTrials.gov
NCT02589028

ABSTRACT

Aims/Introduction: Protein preload improves postprandial glycemia by stimulating secretion of insulin and incretin hormones. However, it requires a large dose of protein to produce a significant effect. The present study was carried out to investigate the postprandial glucose-lowering effect of a premeal protein-enriched, dietary fiber-fortified bar (PFB), which contains moderate amounts of protein, in individuals with type 2 diabetes mellitus or normal glucose tolerance (NGT).

Materials and Methods: The participants (15 type 2 diabetes mellitus and 15 NGT) were randomly assigned to either a premeal or postmeal PFB group and underwent two mixed meal tolerance tests, 1 week apart in reverse order. Plasma levels of glucose, insulin, glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide were measured.

Results: During the mixed meal tolerance tests, the incremental area under the curve from 0 to 180 min of plasma glucose levels was lower with premeal PFB than with postmeal PFB in the type 2 diabetes mellitus (14,723 ± 1,310 mg min/dL vs 19,642 ± 1,367 mg min/dL; $P = 0.0002$) and NGT participants (3,943 ± 416 mg min/dL vs 4,827 ± 520 mg min/dL, $P = 0.0296$). In the type 2 diabetes mellitus participants, insulinogenic index and the incremental area under the curve from 0 to 180 min of plasma total glucagon-like peptide-1 levels were higher with premeal PFB than with postmeal PFB, but not in the NGT participants. There was no difference in postprandial glucose-dependent insulinotropic polypeptide levels between premeal and postmeal PFB in both groups.

Conclusions: Acute administration of premeal PFB decreased postprandial glucose excursion in both type 2 diabetes mellitus and NGT participants. In the type 2 diabetes mellitus participants, premeal PFB augmented the early-phase insulin secretion, possibly through enhancing glucagon-like peptide-1 secretion.

INTRODUCTION

Postprandial hyperglycemia is associated with an increased risk of type 2 diabetes mellitus and cardiovascular disease[1–6]. Postprandial glucose homeostasis is controlled by numerous factors, such as quantity and composition of nutrients, gastric emptying rate, glucose absorption rate, secretion of incretin hormones (glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic polypeptide [GIP]), insulin secretion, glucose uptake by insulin-sensitive tissues and endogenous glucose production[7,8]. Understanding these factors provides therapeutic approaches to improve postprandial hyperglycemia and its adverse consequences. Indeed, alpha-glucosidase inhibitors, which lower postprandial glucose levels, reduced the risk of developing type 2 diabetes mellitus and major cardiovascular events in individuals with impaired glucose tolerance[9–11].

Nutrition therapy is crucial to postprandial glucose control. Evidence is growing that protein preload has a glucose-lowering

Received 7 August 2017; revised 21 November 2017; accepted 26 February 2018

effect in type 2 diabetes mellitus patients and individuals with normal glucose tolerance (NGT)[12–17]. Preload of whey protein, a byproduct of cheese production, reduces postprandial glucose excursion by stimulation of insulin, GLP-1, GIP, cholecystokinin and peptide YY secretion, and by deceleration of gastric emptying and loss of appetite[18]. Soy protein preload also decreased postload glucose levels and increased insulin secretion during a 75-g oral glucose tolerance test in NGT participants[17]. With regard to this notion, meal sequence by consuming fish or meat before carbohydrate-based food has a significant impact on postprandial glucose regulation[19]. Hence, protein preload might be used to control postprandial glycemia.

Protein preload has glucose-lowering and insulinotropic effects in a dose-dependent manner[16,17]. However, the optimal dose of the protein preload balancing glucose-lowering effect, calorie and cost has not been determined. In type 2 diabetes mellitus patients, a 50-g whey protein preload decreased postprandial glucose levels by 28% with a twofold increase in insulin secretion during a 180-min postprandial period[13]. In a study with healthy Japanese participants, 20 g or 40 g of soy protein isolate preload also reduced postprandial glycemia with increasing insulin secretion[17]. However, 50 g of protein corresponds to 200 kcal, and these excess calories might result in other problems, such as weight gain, in some people. In a 4-week study of type 2 diabetes mellitus patients, a 25-g whey protein preload three times a day improved postprandial hyperglycemia with no weight gain[12]. However, long-term effects of caloric surplus provided by premeal protein have not been evaluated.

Dietary fiber might be a good supplement to protein preload. Intake of dietary fiber might improve postprandial glucose excursion by reducing calorie intake, increasing satiety and delaying gastric emptying[20–22]. We previously reported that dietary-fiber-enriched cereal flakes attenuated postprandial hyperglycemia in type 2 diabetes mellitus patients[23]. The effect of dietary fiber on glycemia in type 2 diabetes mellitus patients has been reported as variable, with a mean change in hemoglobin A1c (HbA1c) of −0.55% (95% confidence interval −0.96 to −0.31%)[24]. However, the effect of adding dietary fiber to protein premeal has not yet been thoroughly investigated. In patients with prediabetes and type 2 diabetes mellitus, a preload containing a moderate amount (17 g) of whey protein and 5 g of guar decreased peak and 3-h capillary glucose levels after mixed meal[25]. Therefore, adding dietary fiber to protein premeal is a feasible option to preserve the postprandial glucose-lowering effect while reducing the amount of protein.

In this regard, we developed a protein-enriched, dietary-fiber-fortified bar (PFB) as a premeal for the following reasons: (i) to reduce the protein amount and calorie intake; (ii) to obtain metabolic benefits of dietary fiber; (iii) to reduce production cost; and (iv) to increase palatability. In the present study, we investigated the postprandial glucose-lowering effect of premeal PFB compared with postmeal PFB in type 2 diabetes mellitus patients or individuals with NGT.

METHODS

Participants

The present study included 15 type 2 diabetes mellitus patients and 15 individuals with NGT. Eligible participants were adults aged 18–80 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 no more than 2.5-fold the upper limit of normal range. The type 2 diabetes mellitus patients had been clinically diagnosed with type 2 diabetes mellitus at least 12 weeks before the screening test, and were treated with lifestyle management and/or oral antidiabetic drugs including metformin, sulfonylurea and dipeptidyl peptidase-4 inhibitor as monotherapy or combination therapy. The type 2 diabetes mellitus patients had a HbA1c level of 6.5–10.0% if they were naïve to any glucose-lowering agent, a HbA1c level of 6.0–10.0% if they had taken metformin or sulfonylurea and a HbA1c level of 6.0–9.0% if they had taken a dipeptidyl peptidase-4 inhibitor as combination therapy for at least 12 weeks before randomization. The NGT participants 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[26] at the time of the screening tests. We excluded participants who were diagnosed with type 1 diabetes mellitus or diabetic ketoacidosis; were undergoing insulin therapy; had a history of allergy to flour, nuts, legumes and milk; had a history of gastrointestinal surgery (except hemorrhoidectomy, hernia repair surgery and appendectomy); and women who were pregnant or lactating. This study was registered at ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT02589028). The study protocol was approved by the institutional review board of the Seoul National University Hospital (IRB No. 1307-133-508). All participants provided written informed consent.

Study design and procedures

This was a randomized, open-label study. Eligible participants visited the Clinical Trial Center of Seoul National University Hospital, Seoul, Korea, at 08.30 hours after an overnight (10 h) fast on 2 separate days, 1 week apart and underwent the mixed meal tolerance test (MMTT). The participants stopped taking metformin or sulfonylurea the day before the first visit, and dipeptidyl peptidase-4 inhibitor 1 week before the first visit. The participants were randomly assigned to two groups and had PFB followed by breakfast (premeal PFB) or breakfast followed by PFB (postmeal PFB). In the premeal PFB studies, the participants started to eat PFB at −30 min (08.30 hours) before the test meal (09.00 hours). In the postmeal PFB studies, the participants started to eat the test meal at 0 min (09.00 hours) and consumed PFB at the end of the test meal. A PFB was provided with 150 mL of water. The participants were instructed to eat the test meals and PFB, both within 15 min. After 1 week, the participants were provided with PFB and breakfast in reverse order (Figure 1). The PFB was made by

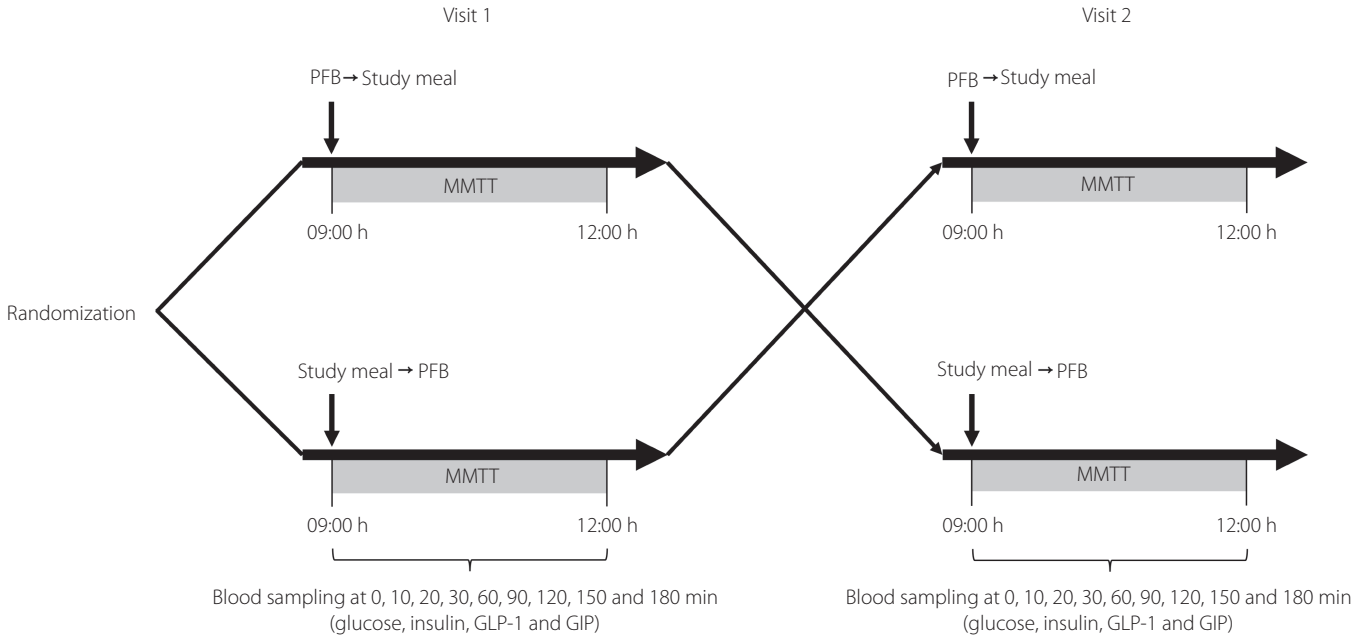

Figure 1 | Study design and procedures. The study participants underwent the mixed meal tolerance test on 2 separate days, 1 week apart. The participants were randomly assigned to two groups and had a protein-enriched, dietary fiber-fortified bar (PFB) followed by breakfast (premeal PFB) or breakfast followed by a PFB (postmeal PFB). After 1 week, the participants were provided with a PFB and breakfast in the reverse order. GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; MMTT, mixed meal tolerance test.

Ssial Food, Inc. (Jecheon, Korea). One serving of PFB (30 g) had 73 kcal, and contained 0.4 g of carbohydrate, 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%), glycerin fatty acid esters (0.4%), stevia (0.6%), indigestible maltodextrin (25.8%), D-sorbitol (6.4%), citric acid (0.1%) and vanilla extract (0.1%). Breakfast was a standardized high-glycemic index diet. The nutrition facts of a study meal are detailed in Table 1.

After measuring height and bodyweight, an 18-G indwelling intravenous catheter was placed in the forearm. Venous blood samples were collected at -30, 0, 10, 20, 30, 60, 90, 120, 150 and 180 min during the MMTT. Serum and plasma were separated immediately by centrifugation at 500 *g*, 4°C for 15 min, and stored at −70°C until analyzed.

Table 1 | Composition and nutrition facts of protein-enriched, dietary fiber-fortified bar and a study meal

	Protein-enriched, dietary fiber-fortified bar	Study 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	–	–	–

Measurements

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 carried out according to the manufacturer's instructions.

Study end-points

The primary end-point was the difference in the incremental area under the curve (iAUC) of plasma glucose levels between 180-min MMTTs with premeal and postmeal PFB in the type 2 diabetes mellitus or NGT participants. The secondary end-points were differences in the iAUC of plasma levels of insulin, total GLP-1 and total GIP between 180-min MMTTs with premeal and postmeal PFB in the type 2 diabetes mellitus or NGT participants.

Sample size calculation

The number of participants was based on the iAUC of plasma glucose concentrations reported in the previous study[27], assuming a difference of 290 mmol min/L and a standard deviation

of 255 mmol min/L between premeal and postmeal PFB, with a power of 80% and a type I error of 0.05. Considering a drop-out rate of 20%, 15 participants were recruited in the type 2 diabetes mellitus and NGT groups, respectively.

Statistical analysis

Continuous variables are presented as the 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 min were analyzed by two-way repeated measures ANOVA. The iAUC of plasma glucose, insulin, total GLP-1, total GIP and glucagon levels were calculated according to the trapezoid rule and analyzed by the paired *t*-test. Insulinogenic index (IGI) was calculated as (insulin 30 min − insulin 0 min)/(glucose 30 min − glucose 0 min). 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

A total of 31 participants were screened for the present study, but one participant with NGT was excluded because of fasting hyperglycemia. Finally, 30 participants (15 participants with type 2 diabetes mellitus and NGT, respectively) completed the study with no adverse events, including gastrointestinal symptoms. In the type 2 diabetes mellitus participants, the average age was 62.9 ± 4.3 years, BMI was 24.8 ± 3.5 kg/m^2 and HbAlc level was 6.8 ± 0.4%. The mean duration of type 2 diabetes mellitus was 13.8 ± 6.7 years, and all the type 2 diabetes mellitus participants were taking at least one oral antidiabetic drug, including metformin. In the NGT participants, the average age was 47.3 ± 9.8 years, BMI was 23.1 ± 3.1 kg/m^2 and HbA1c level was 5.3 ± 0.3%. Additional information about the results of baseline laboratory tests and medical history is described in Table 2.

Table 2 | Baseline characteristics of the study participants

	Type 2 diabetes mellitus (*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
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
Duration of type 2 diabetes mellitus (years)	13.8 ± 6.7	–	NA
Patients taking glucose-lowering agents (*n*)	15	–	NA
Metformin	7	–	NA
Metformin + SU	4	–	NA
Metformin + DPP-4 inhibitor	2	–	NA
Metformin + SU + DPP-4 inhibitor	2	–	NA
Hypertension (*n*)	6	0	<0.001
Dyslipidemia (*n*)	6	0	<0.001

Data are shown as mean ± standard deviation or the number of participants. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not applicable; NGT, normal glucose tolerance; SU, sulfonylurea.

In the type 2 diabetes mellitus participants, the $iAUC_{0–180}$ of plasma glucose levels, which was the primary end-point of the present study, was significantly lower with premeal PFB than with postmeal PFB (14,723 ± 1,310 mg min/dL vs 19,642 ± 1,367 mg min/dL, $P = 0.0002$; Figure 2c). Postprandial plasma glucose levels tended to be lower with premeal PFB than with postmeal PFB in the type 2 diabetes mellitus participants (Figure 2a). In the NGT participants, the $iAUC_{0–180}$ of plasma glucose levels was significantly lower with premeal PFB than postmeal PFB (3,943 ± 416 mg min/dL vs 4,827 ± 520 mg min/dL, $P = 0.0296$; Figure 2c). Plasma glucose levels were significantly lower with premeal PFB than postmeal PFB at 30 min (122 ± 4 mg/dL vs 146 ± 5 mg/dL, $P = 0.001$) and 60 min (118 ± 5 mg/dL vs 138 ± 7 mg/dL, $P = 0.007$) after a study meal of the NGT participants (Figure 2b). Premeal PFB did not affect the 0-min plasma glucose levels in the participants with type 2 diabetes mellitus or NGT (Figure 2a,b).

In the type 2 diabetes mellitus participants, the $iAUC_{0–180}$ of plasma insulin levels was significantly lower with premeal PFB than with postmeal PFB (4,898 ± 677 uIU min/mL vs 6,680 ± 986 uIU min/mL, $P = 0.0019$; Figure 3c). Intriguingly, however, premeal PFB induced early-phase insulin secretion by shifting the insulin curve to the left compared with postmeal PFB in the type 2 diabetes mellitus participants (Figure 3a). The insulin secretion of the type 2 diabetes mellitus participants tended to be higher with premeal PFB than with postmeal PFB in the early postprandial period and lower in the late postprandial period. Plasma insulin levels were significantly lower with premeal PFB than with postmeal PFB at 150 min after a study meal of the type 2 diabetes mellitus participants (39.8 ± 5 μIU/mL vs 59.7 ± 8 μIU/mL, $P = 0.001$; Figure 3a). IGI was significantly higher with premeal PFB than with postmeal PFB in the type 2 diabetes mellitus participants (0.53 ± 0.43 vs 0.28 ± 0.16, $P = 0.0166$; Figure 3d). In the NGT participants, the $iAUC_{0–180}$ of plasma insulin levels was significantly lower with premeal PFB than with postmeal PFB (7,217 ± 1,201 uIU min/mL vs 9,664 ± 1,558 uIU min/mL, $P = 0.0039$; Figure 3c).

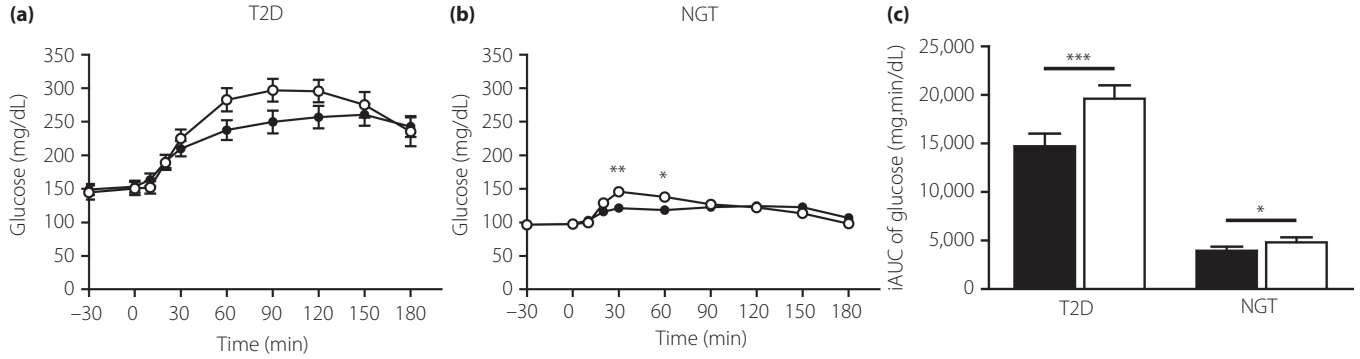

Figure 2 | Postprandial glucose levels in the participants with type 2 diabetes mellitus and normal glucose tolerance (NGT). Postprandial glucose levels were measured during the mixed meal tolerance test in the type 2 diabetes mellitus and NGT participants. (a) Postprandial glucose levels in the type 2 diabetes mellitus patients. (b) Postprandial glucose levels in the NGT participants. (c) The incremental area under the curve (iAUC) from 0 to 180 min of plasma glucose levels in the type 2 diabetes mellitus and NGT participants. Black circle/bar, premeal bar; white circle/bar, postmeal bar. Two-way repeated measures ANOVA was used to determine statistical significance. The iAUCs of plasma glucose levels were calculated according to the trapezoid rule and analyzed by paired *t*-test. Data are shown as the mean ± standard error of the mean. **P* < 0.05, ***P* < 0.01, ****P* < 0.001.

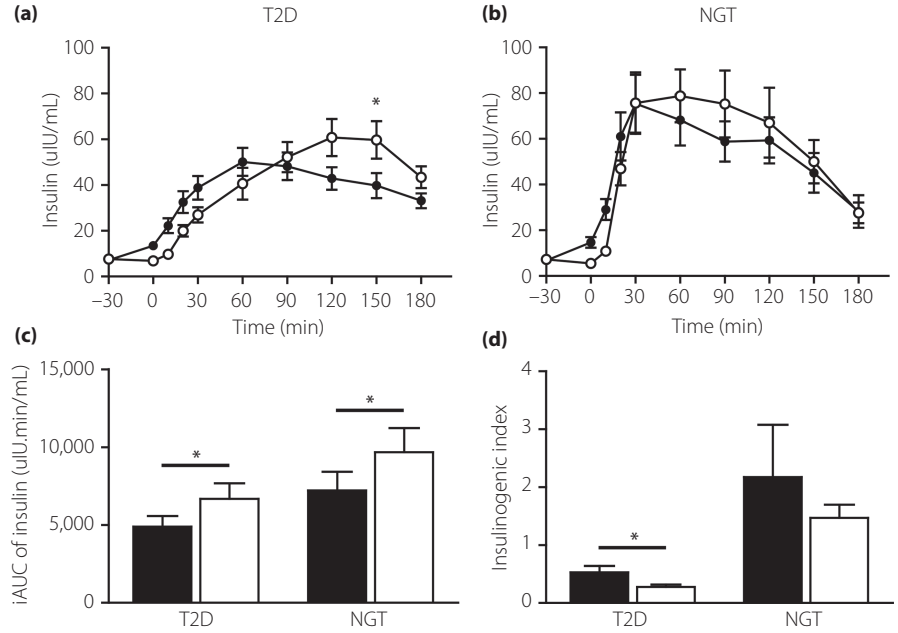

Figure 3 | Postprandial insulin levels and insulinogenic index (IGI) in the participants with type 2 diabetes mellitus and normal glucose tolerance (NGT). Postprandial insulin levels were measured during the mixed meal tolerance test in the type 2 diabetes mellitus and NGT participants. (a) Postprandial insulin levels in the type 2 diabetes mellitus participants. (b) Postprandial insulin levels in the NGT participants. (c) The incremental area under the curve (iAUC) from 0 to 180 min of plasma insulin levels in the type 2 diabetes mellitus and NGT participants. IGI was calculated as (insulin 30 min – insulin 0 min)/(glucose 30 min – glucose 0 min). (d) IGI in the type 2 diabetes mellitus and NGT participants. Black circle/bar, premeal bar; white circle/bar, postmeal bar. Two-way repeated measures ANOVA was used to determine statistical significance. The iAUCs of plasma insulin levels were calculated according to the trapezoid rule and analyzed by paired *t*-test. IGI was analyzed by paired *t*-test. Data are shown as the mean ± standard error of the mean. **P* < 0.05.

However, there was no shift in the insulin curve and no difference in IGI (2.18 ± 0.90 vs 1.47 ± 0.88, $P = 0.4215$) between premeal and postmeal PFB in the NGT participants (Figure 3b,d).

In the type 2 diabetes mellitus participants, the $iAUC_{0–180}$ of plasma total GLP-1 levels was significantly higher with premeal PFB than with postmeal PFB (2,759 ± 413 pM min vs 1,712 ± 249 pM min, $P = 0.0020$; Figure 4c). There was no

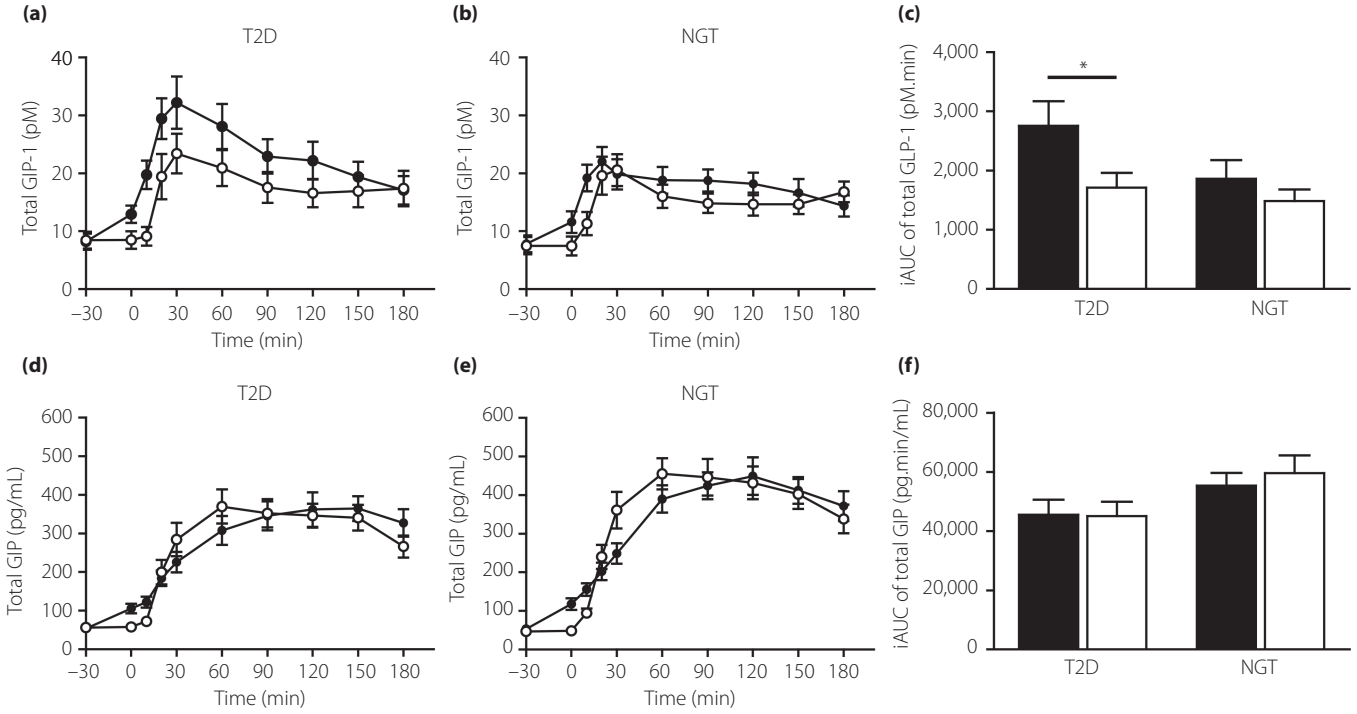

Figure 4 | Postprandial total glucagon-like peptide-1 (GLP-1) and total glucose-dependent insulinotropic polypeptide (GIP) levels in the participants with type 2 diabetes mellitus and normal glucose tolerance (NGT). Postprandial total GLP-1 and GIP levels were measured during the mixed meal tolerance test in the type 2 diabetes mellitus and NGT participants. (a) Postprandial total GLP-1 levels in the type 2 diabetes mellitus participants. (b) Postprandial total GLP-1 levels in the NGT participants. (c) The incremental area under the curve from 0 to 180 min ($iAUC_{0–180}$) of plasma total GLP-1 levels in the type 2 diabetes mellitus and NGT participants. (d) Postprandial total GIP levels in the type 2 diabetes mellitus participants. (e) Postprandial total GIP levels in the NGT participants. (f) The $iAUC_{0–180}$ of plasma total GIP levels in the type 2 diabetes mellitus and NGT participants. Black circle/bar, premeal bar; white circle/bar, postmeal bar. Two-way repeated measures ANOVA was used to determine statistical significance. The iAUCs of plasma total GLP-1 and total GIP levels were calculated according to the trapezoid rule and analyzed by the paired *t*-test. Data are shown as the mean ± standard error of the mean. *$P < 0.05$.

difference in the $iAUC_{0–180}$ of plasma total GIP levels between premeal and postmeal PFB in the type 2 diabetes mellitus participants (45,520 ± 5,018 pg min/mL vs 45,010 ± 4,900 pg min/mL, $P = 0.8210$; Figure 4f). In the NGT participants, the $iAUC_{0–180}$ of plasma total GLP-1 (1,860 ± 314 pM min vs 1,484 ± 199 pM min, $P = 0.0857$; Figure 4c) and total GIP levels (55,380 ± 4,317 pg min/mL vs 59.580 ± 5,976 pg min/mL, $P = 0.1406$; Figure 4f) were not different between premeal PFB and postmeal PFB, respectively.

DISCUSSION

We found that premeal PFB reduced postprandial glucose excursions after a standard test meal in the type 2 diabetes mellitus or NGT participants. Previously, a single dose of 50-g whey protein or 4-week treatment with 25-g whey protein three times a day improved postprandial hyperglycemia when given before a mixed meal[12,13]. However, weight gain as a result of calorie surplus might be a potential problem of consuming a large amount of premeal protein. In a dose-response study, 10 g, 20 g and 40 g of whey protein preload reduced the glycemic response by 29%, 47% and 64%, respectively, after consuming pizza of 12 kcal/kg bodyweight[15]. As the glucose-lowering effect of protein preload is dose-dependent, it is important to determine the minimum effective dose of protein. To preserve the postprandial glucose-lowering effect while reducing the amount of protein, we added dietary fiber (12.7 g) to protein (10.7 g) in the form of a bar. Overall, we showed that premeal intake of the PFB improved postprandial glycemic response in the type 2 diabetes mellitus or NGT participants.

In the type 2 diabetes mellitus patients, the glucose-lowering effect of premeal PFB was associated with an increase of early-phase insulin secretion, which was shown by increased IGI and a left shift in the plasma insulin curve during the MMTT. In contrast, postprandial insulin secretion during the MMTT was lower with premeal PFB than with postmeal PFB. These findings denote that the early-phase insulin secretion is more critical to control postprandial hyperglycemia than total insulin secretion. Early-phase insulin secretion plays an important role in the normal suppression of endogenous glucose production after meal ingestion[28], and the loss of this secretory response contributes to postprandial hyperglycemia in type 2 diabetes mellitus patients[29]. In addition, in the present study, early-phase

insulin secretion was accompanied by enhanced GLP-1 secretion in the type 2 diabetes mellitus patients. In this regard, it is noteworthy that GLP-1 receptor knockout mice showed lower plasma insulin levels in the early phase of an oral glucose tolerance test compared with wild-type mice[30]. In a study of type 2 diabetes mellitus patients, decreased early insulin secretion was associated with diminished GLP-1 response during the MMTT[31]. A previous study showed that whey protein preload in type 2 diabetes mellitus patients improved postprandial hyperglycemia by increasing both early- and late-phase insulin and GLP-1 secretion during the MMTT compared with a placebo (water preload)[13]. In the present study, the increase of the late-phase insulin secretion observed in the postmeal PFB group might be due to PFB consumption after test meals. These findings showed that early-phase insulin secretion by premeal PFB was more important to improve postprandial hyperglycemia than late-phase insulin secretion by postmeal PFB. In the NGT participants, however, no difference was found in the IGI between premeal PFB and postmeal PFB studies. As postprandial GLP-1 secretion was not different between premeal PFB and postmeal PFB in the NGT participants, increased early insulin responses to premeal PFB found in the type 2 diabetes mellitus patients might be due to the exaggerated GLP-1 responses.

In contrast, premeal PFB might reduce the postprandial glycemic response by its effect on the gastric emptying rate, which was unfortunately not measured in the present study. It was reported that gastric emptying accounted for up to 35% of the variance in the initial rise and peak postprandial glucose levels in type 2 diabetes mellitus or NGT particiapnts[32]. Whey protein preload slowed the gastric emptying rate compared with water or glucose preload[33,34]. Dietary fiber might also affect the gastric emptying rate. However, the effects of dietary fiber on gastric emptying are diverse[35–38]. In general, a high dose of fiber (≥7 g) tends to delay gastric emptying, whereas a low dose of fiber does not have a significant effect on gastric emptying[39]. Increased viscosity of gastric contents as a result of dietary fiber decreases pyloric flow by reducing the separation of solids from liquids[40]. Further investigation is required to evaluate the effect of PFB on gastric emptying in type 2 diabetes mellitus patients or individuals with NGT.

Premeal PFB stimulated postprandial GLP-1 secretion during the MMTT in the type 2 diabetes mellitus patients, but not in the NGT participants. This result is inconsistent with previous findings of reduced GLP-1 secretion after an oral glucose tolerance test or MMTT in type 2 diabetes mellitus patients compared with individuals with NGT[41,42]. However, reports have shown that the GLP-1 secretory response was not different between type 2 diabetes mellitus and NGT participants after balancing age, BMI, plasma glucagon and fasting non-esterified fatty acids concentrations[42,43]. In the present study, the type 2 diabetes mellitus patients were older than the NGT participants, and the BMIs were not different between the two groups. Notably, all the type 2 diabetes mellitus patients in the present study had been taking metformin until the day before the study. Metformin stimulates GLP-1 secretion by preventing intestinal absorption of bile acids with subsequent activation of the G protein-coupled bile acid receptor 1 (TGR5) and decreased activation of the farnesoid X receptor in L cells[44–46]. In addition, metformin alters the composition of gut microbiota, reduces the lipotoxicity of L cells, stimulates the parasympathetic nervous system, increases GLP-1 sensitivity of β-cells and might prolong the half-life of active GLP-1[47–51]. Therefore, it is conceivable that the effect of premeal PFB on GLP-1 secretion might differ depending on the use of metformin, which needs to be addressed in future studies.

Premeal PFB had no effect on postprandial GIP secretion during the MMTT in the type 2 diabetes mellitus or NGT participants. A meta-analysis showed there was no difference in GIP secretion between NGT and type 2 diabetes mellitus participants[52]. Unlike GLP-1 secretion, metformin does not affect GIP secretion, both in rodents and humans[53,54]. As GIP stimulates glucagon secretion and might promote fat accumulation[55], the neutral effect of premeal PFB on GIP secretion might be beneficial.

The present study had the following limitations. First, we evaluated only the effect of single administration of premeal PFB on postprandial glucose excursions in the type 2 diabetes mellitus and NGT participants. Long-term studies with premeal PFB are required to ascertain if it can reduce HbA1c and improve diabetes management. Second, we did not compare the effect of protein and dietary fiber separately on postprandial glycemic and hormonal responses. Third, we did not carry out dose–response studies with various doses of protein and dietary fiber. Finally, the gastric emptying rate, appetite and food intake, which play an important role in the regulation of postprandial glucose homeostasis, were not evaluated in the present study.

In conclusion, acute administration of the premeal PFB improved postprandial glucose excursions in the type 2 diabetes mellitus and NGT participants. Although the mechanism of action and long-term effect need to be investigated, the PFB could be a non-pharmacological way to improve postprandial glucose metabolism.

ACKNOWLEDGMENT

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Korea (grant number: HI14C1277).

DISCLOSURE

The authors declare no conflict of interest.

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