Attenuation of Lipid Metabolism by Novel Pleiotropic Effects of Konjac Glucomannan

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Research

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Abstract

Background: Recently, we showed that konjac glucomannan (KGM) inhibited rice gruel-induced postprandial elevation of plasma glucose and insulin. To extend that research, we investigated the effects of adding KGM to rice gruel on pre- and postprandial circulating lipoprotein lipase (LPL), glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1), and triglyceride concentrations.

Methods: Twenty-four Japanese male subjects without diabetes or gastrointestinal diseases (aged 46–56 years) were included. Subjects received rice gruel containing 0% or 0.8% of KGM (0%G and 0.8%G, respectively). Blood samples were obtained at preload and 30, 60, and 120 min after receiving rice gruel with or without 0.8% KGM. LPL, GPIHBP1, and triglyceride concentrations in these samples were measured.

Results: Circulating triglycerides were significantly reduced at 30 min and then returned to the fasting value in the subjects who received 0%G, whereas lower triglyceride levels were sustained in those who received 0.8%G. Although circulating levels of LPL and GPIHBP1 were significantly reduced for 0%G, they were increased for 0.8%G. We found a significant negative correlation between circulating levels of fasting LPL and triglycerides and a significant positive correlation between circulating levels of fasting LPL and GPIHBP1. A significant negative correlation between circulating levels of triglycerides at 120 min and fasting LPL was shown in the 0.8%G group, but not in the 0%G group. A significant positive correlation between circulating levels of LPL at 0 min and 120 min was shown in the 0%G and 0.8%G groups.

Conclusions: The results demonstrated a novel pleiotropic effect of KGM. Supplementation of KGM powder in rice gruel sustained lower levels of triglycerides accompanying elevation of LPL and GPIHBP1, which attenuated lipid metabolism. Additionally, fasting LPL is a predictor of postprandial circulating levels of LPL.

Trial registration: UMIN registration number: UMIN000025950; registered at February 1st. 2017; https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000029247

Background

Konjac glucomannan (KGM) is a rich source of soluble fiber containing almost no calories [1]. Since KGM has good biocompatibility and biodegradable properties, it is widely used as a medicinal material and traditional food in the form of konjac jelly, noodles, and tofu [2–6]. As summarized by Devaraj et al., KGM has significant roles in the treatment and prevention of various diseases because of its pleiotropic effects, such as anti-diabetic, anti-obesity, anti-inflammatory, prebiotic activity, natural antibiotics, immune system regulatory, and laxative effects [7]. The major health benefits of KGM include lowering of blood glucose, cholesterol, triglyceride, blood pressure, and body weight by promoting intestinal activity and boosting immune functions in humans [2, 6, 7]. In these investigations, the study subjects habitually

ingested KGM every day for 8 weeks [2, 6, 7]. KGM absorbs digested body waste in the stomach and intestine by entrapping it within a gelatinous mass, which is eliminated from the body without being absorbed. KGM acts as a barrier to absorption of sugars and nutrients because of its viscosity produced in the gastrointestinal compartments [7].

In Japan, KGM is abundant, easily accessible, and incorporated into various food products. Despite its considerable popularity in Japan, only a few studies have demonstrated the immediate suppression of postprandial glucose, insulin, and lipid parameters in subjects with normal or impaired glucose tolerance. Our previous study was the first to demonstrate that intake of rice gruel containing KGM suppressed postprandial elevation of circulating glucose and insulin [8]. Extending our previous research, we planned to investigate the immediate effect of KGM on postprandial triglycerides and related lipase, lipoprotein lipase (LPL), and its glycolipid-anchored protein named glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1). LPL is the central molecule in plasma lipid metabolism, hydrolyzing triglycerides within triglyceride-rich lipoproteins (TRLs) and releasing lipid nutrients for vital tissues (e.g., heart, skeletal muscle, and adipose tissue) [9]. Genetic variation altering the efficiency of LPL-mediated TRL processing influences both plasma triglyceride levels and the risk for coronary heart disease [10, 11]. GPIHBP1 is solely responsible for capturing LPL within the interstitial spaces and shuttling it across endothelial cells to its site of action in the capillary lumen [12]. GPIHBP1-bound LPL is required for the margination of TRLs along capillaries, allowing the lipolytic processing of TRLs to proceed [13]. Missense mutations that interfere with LPL–GPIHBP1 interactions profoundly impair intravascular triglyceride processing, resulting in severe hypertriglyceridemia [14, 15]. Fasting LPL mass levels may be useful as a predictor of postprandial triglyceride increases in fasting normotriglyceridemic subjects, and fasting LPL mass is a simple easy-to-use marker that can be applied in clinical practice [16]. On the other hand, no significant increase in LPL activity was found during chylomicron and very low-density lipoprotein (VLDL) overload after different kinds of food intake [17]. These findings led us to ask what ingredients in food, such as KGM, increase circulating LPL. The study aim was to investigate the pre- and post-load triglyceride, LPL and GPIHBP1 levels among individuals receiving rice gruel with or without KGM.

Materials And Methods

Participants

This study is additional analysis of the former article, which demonstrated that intake of rice gruel containing KGM suppressed postprandial elevation of circulating glucose and insulin [8]. Twenty-four participants provided written informed consent, and the Gunma University Ethical Review Board for Medical Research Involving Human Subjects approved the study protocol (UMIN registration number: UMIN000025950). A total of 24 Japanese subjects (all males) participated in this study. The characteristics of all 24 participants are presented in Table 1. None of the participants had diabetes, gastrointestinal diseases or statin treatment (Fig. 1).

Table 1
Characteristics of the 24 participants

	All participants (n = 24)		
Age (years)	49.7	±	6.7
Weight (kg)	76.6	±	9.5
BMI (kg/m^2)	25.9	±	2.8
Systolic blood pressure (mm Hg)	130.7	±	13.5
Diastolic blood pressure (mm Hg)	82.0	±	10.0
Fasting plasma glucose (mg/dL)	104.0	±	7.5
Fasting plasma insulin (U/mL)	6.7	±	3.3
HbA1c (%)	5.6	±	0.27
LDL-C (mg/dL)	121.5	±	28.4
HDL-C (mg/dL)	47.2	±	9.4
Triglyceride (mg/dL)	188.3	±	186.1
FFA (μEq/L)	518.1	±	205.4
LPL (ng/mL)	51.3	±	19.2
GPIHBP1 (pg/mL)	902.7	±	210.2
HTGL (pg/mL)	73.3	±	23.4

Abbreviations used: BMI, body mass index; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FFA, free fatty acid; LPL, lipoprotein lipase; GPIHBP1, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1; HTGL, hepatic triglyceride lipase.

Test Gruel

Three types of gruel were used for testing: KGM-free rice gruel (0%G), rice gruel containing 0.4%, or 0.8% KGM powder (0.4%G and 0.8%G, respectively). All of the rice gruel preparations were provided by GREEN LEAF Co., Ltd. (Akagihara, Showa, Gunma, Japan). Each type of gruel weighed 250 g, with 0%G, 0.4%G, and 0.8%G containing 75, 77, and 80 kcal, respectively [8].

Study Design

After the 75 g oral glucose tolerance test (75gOGTT), none of 24 participants were diagnosed of diabetes, therefore 24 subjects underwent three tests weekly. Each test involved subjects being fed any of the three

types of gruel followed by blood sampling, as with the 75gOGTT. All 24 participants ingested three concentrations of KGM (0%, 0.4%, and 0.8%) in rice gruel within 3 weeks. To perform a double-blind randomized trial, we prepared six protocols for the gruel tolerance test in this study, as described in Fig. 1. All of the 24 patients were randomly allocated to one of the six protocols. Blood sampling was performed to establish the plasma glucose and immunoreactive insulin levels at preload and 30, 60, and 120 min after ingesting gruel. Similarly, serum HDL-C, LDL-C, triglycerides, and HbA1c were also measured during preload [8]. After these measurements, the remaining samples underwent additional analysis. We measured triglycerides, free fatty acid (FFA), LPL, GPIHBP1, and hepatic triglyceride lipase (HTGL) in the remaining 0%G and 0.8%G samples (Fig. 1).

Laboratory Assays

Serum HDL-C, LDL-C, triglycerides, and FFA concentrations were measured by using enzymatic methods (LABOSPECT 008; Hitachi, Tokyo), and serum insulin concentrations were measured by chemiluminescence immunoassay (AIA-2000 LA; Tosoh, Tokyo). Plasma glucose concentrations were measured by using a hexokinase method (ADAMS Glucose GA-1170; Arkray, Tokyo), and HbA1c levels were measured by high-performance liquid chromatography (ADAMS A1c HA8180; Arkray). Serum LPL concentrations were measured by using an LPL assay kit (SEKISUI MEDICAL CO. LTD, Tokyo) based on a sandwich enzyme-linked immunosorbent assay (ELISA) [18]. A Human GPIHBP1 Assay Kit and a Human Serum HTGL ELISA Kit (Immno-Biological Laboratories Co., Ltd., Gunma) based on ELISA were used to determine serum GPIHBP1 and HTGL concentrations, respectively [18].

Statistical analysis

Statistical analyses were performed by using the SPSS ver. 25 statistical software package (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY). Data are expressed as the mean ± standard deviation. The effects of time (change from baseline) on blood glucose, plasma insulin, triglycerides, LPL, GPIHBP1, and HTGL concentrations were analyzed by using two-way repeated analysis of variance. When a significant effect was detected, the Dunnett and Tukey post hoc tests were performed to determine the effects of time and treatment, respectively. Statistical significance was set at $p < 0.05$.

Results

Changes in the circulating triglyceride levels in the gruel tolerance test

Significant reduction of circulating FFA was detected after intake of rice gruel with or without KGM supplementation. The serum levels of FFA in the subjects who received 0%G and 0.8%G were significantly lower at 30, 60, and 120 min than at 0 min (Fig. 2A). No significant differences in serum levels of FFA were observed between the 0.8%G group and 0%G group at 0, 30, 60, and 120 min, respectively (Fig. 2A).

Intake of rice gruel significantly reduced circulating levels of triglycerides promptly and returned to a preload value immediately in the 0%G group (Fig. 2B). Circulating levels of triglycerides in the 0.8%G group were significantly lower at 30, 60, and 120 min than at 0 min (Fig. 2B). These results indicated that KGM supplementation in rice gruel was significantly associated with lower circulating levels of triglycerides than fasting levels of triglycerides (Fig. 2B). Circulating levels of triglycerides at 0, 30, 60, and 120 min were significantly higher in the 0.8%G group than in the 0%G group (Fig. 2B). These differences might have been caused by difficulty in managing eating habits during this study. The participants stayed and ate each domestic meal at their homes during the 3 weeks of this study.

Changes in the circulating LPL, GPIHBP1, and HTGL levels in the gruel tolerance test

The circulating levels of LPL in the 0%G group were significantly lower at 30, 60, and 120 min than at 0 min (Fig. 2C). In contrast, the circulating levels of LPL in the 0.8%G group were significantly higher at 120 min than at 0 min (Fig. 2C). The circulating levels of LPL were significantly higher in the 0%G group than in the 0.8%G at 0 min (Fig. 2C). In the 0%G, the circulating levels of GPIHBP1 were significantly lower at 30, 60, and 120 min than at 0 min (Fig. 2D). In contrast, the circulating levels of GPIHBP1 in the 0.8%G group were significantly higher at 60 and 120 min than at 0 min (Fig. 2D). There were no significant differences in the circulating levels of HTGL at 0, 30, 60, and 120 min between the 0%G and 0.8%G groups (Fig. 2E).

Circulating levels of fasting LPL were significantly correlated with GPIHBP1 and triglycerides

To analyze associations between circulating levels of fasting triglycerides and LPL/ GPIHBP1, we combined the data of preload circulating levels of 0%G and 0.8%G. Therefore, the subjects number in Table 2 was 48. We found a significant negative correlation between circulating levels of fasting LPL and triglycerides and a significant positive correlation between circulating levels of fasting LPL and GPIHBP1 (Table 2). Circulating levels of fasting GPIHBP1 were significantly correlated with LPL and HbA1c (Table 2). No significant correlation was detected between circulating levels of fasting HTGL and metabolic markers of lipid and glucose (Table 2). A significant negative correlation between circulating levels of triglycerides at 120 min and fasting LPL was shown in the 0.8%G group, but not in the 0%G group (Figs. 3B and A, respectively). A significant positive correlation between circulating levels of LPL at 0 min and 120 min was shown in the 0%G and 0.8%G groups (Figs. 3C and D, respectively).

Table 2
Spearman's correlation analyses between LPL, GPIHBP1, and HTGL concentrations and clinical variables at 0 min.

	LPL			GPIHBP1			HTGL	
Variable (n = 48)	ρ	*p*		ρ	*p*		ρ	*p*
Glucose (mg/dL)	−0.125	0.396		0.109	0.463		−0.217	0.138
Insulin (μU/mL)	−0.271	0.062		0.078	0.598		0.062	0.677
HbA1c (%)	−0.007	0.962		0.321	0.026	*	0.010	0.948
LDL-C (mg/dL)	−0.244	0.095		0.029	0.844		0.223	0.128
HDL-C (mg/dL)	0.150	0.308		−0.279	0.055		−0.268	0.066
TG (mg/dL)	−0.515	< 0.001	*	−0.044	0.768		0.063	0.672
FFA (μEq/L)	−0.158	0.283		0.042	0.776		−0.189	0.197
LPL (ng/mL)				0.316	0.029	*	−0.022	0.884
GPIHBP1 (pg/mL)	0.316	0.029	*				0.085	0.566
HTGL (pg/mL)	−0.022	0.884		0.085	0.566			

Abbreviations used: BMI, body mass index; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FFA, free fatty acid; LPL, lipoprotein lipase; GPIHBP1, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1; HTGL, hepatic triglyceride lipase.

Discussion

This study investigated the effects of KGM supplementation on postprandial changes in circulating levels of lipid parameters, including triglycerides, FFA, LPL, GPIHBP1, and HTGL, among middle-aged Japanese subjects. The study results showed that intake of rice gruel containing KGM powder decreased circulating levels of triglycerides accompanying elevation of LPL/GPIHBP1, which has not been previously reported.

Our previous study showed that intake of rice gruel containing KGM powder suppressed postprandial increases in both plasma glucose and insulin [8]. These findings could be explained by reduction of glucose absorption caused by KGM supplementation. However, the finding that KGM supplementation

induced a decrease in triglycerides and an increase in LPL/GPIHBP1 could not be explained by inhibition of lipid absorption.

In previous human and animal studies, habitual supplementation with KGM lowered plasma glucose, triglycerides, and cholesterol, as reviewed by Devaraj et al. [7]. The hypolipidemic effect of KGM supplementation was explained by two mechanisms [2–7]: First, KGM absorbs digested body waste in the stomach and intestine by entrapping it within a gelatinous mass, which is eliminated from the body without being absorbed. The gelatinous nature of KGM in the body provides a sense of satiety and fullness and promotes peristalsis, thus regularizing bowel movements. KGM acts as a barrier to absorption of sugars and nutrients because of its viscosity produced in the gastrointestinal compartments [1–8, 20–26]. KGM supplementation has also been reported to inhibit cholesterol absorption in the jejunum [22] and bile acid absorption in the ileum [23], which contribute to improvements in serum lipid regulation [21]. The second mechanism underlying the hypolipidemic effect of KGM supplementation is inhibition of hepatic cholesterol synthesis. Soluble fibers are fermented by bacteria in the colon, which forms gases and short-chain fatty acids. The short-chain fatty acids are almost completely absorbed into the portal vein and could affect hepatic cholesterol synthesis [27]. The present study added a third mechanism underlying the hypolipidemic effect of KGM: reduction of triglycerides by elevation of circulating LPL/GPIHBP1. The intravascular processing of TRLs by the LPL–GPIHBP1 complex is crucial for clearing triglycerides from the bloodstream and for the delivery of lipid nutrients to vital tissues [9–15, 28]. In our rice gruel tolerance test, serum levels of triglycerides were significantly decreased in the first 30 min and thereafter recovered to preload levels at 60 and 120 min in the 0%G group. Supplementation with 0.8% KGM in rice gruel maintained lower levels of circulating triglycerides at 60 and 120 min. This phenomenon was accompanied by elevation of circulating levels of LPL/GPIHBP1. These results indicate that the effect of reduction of circulating triglycerides at 30 min induced by rice gruel while lower levels of triglycerides were maintained was induced by LPL/GHPIHBP1 elevation. In this study, the elevation in GHPIHBP1 was faster than the elevation in LPL, which suggests that KGM-induced LPL elevation was caused by elevation in GPIHBP1. Additionally, we observed significant negative correlations between circulating levels of fasting LPL and triglycerides. The circulating levels of fasting LPL were positively correlated with LPL at 120 min in both the 0%G and 0.8%G groups and negatively correlated with triglycerides at 120 min in the 0.8%G group, but not in the 0%G group. Consistent with these results, we showed that circulating fasting LPL level was a predictor of LPL activity and circulating LPL level during heparin treatment [17, 29–32]. Tsuzaki et al. reported supportive findings. They found that fasting LPL mass levels may be useful as a predictor of increased postprandial triglycerides and that fasting LPL mass is a simple and easy-to-use marker in clinical practice [16]. On the other hand, no significant increase in LPL activity was found during chylomicron and VLDL overload after different kinds of food intake [17]. These discrepancies could be explained by differences in blood sampling time or test meals. KGM is a rich source of soluble fiber [1] and regulates gastrointestinal and bowel movements by its viscosity and gelatinous nature [2–7].

A reciprocal relationship between intracellular lipolysis and the efficiency of LPL-mediated fat storage was shown in previous studies [33, 34]. In the fed state, intracellular lipase activity is low, and the flow

gradient is inward, promoting efficient uptake of LPL-generated fatty acids. These fatty acids taken up by adipose tissue are directed toward esterification and ultimately triglyceride storage. In the fasting state, intracellular lipase activity is higher, and the gradient of flow tends to be outward, promoting spillover [33, 34]. In agreement with a previous report, circulating levels of FFA were significantly decreased after the intake of rice gruel with or without KGM. On the one hand, reduction of circulating levels of triglycerides was accompanied by LPL/GPIHBP1 elevation. This phenomenon might be explained by efficient uptake of LPL-generated fatty acids in the fed state [33, 34]. Additionally, KGM supplementation might sustain efficient uptake of LPL-generated fatty acids over 120 min.

There was no significant change in circulating HTGL concentrations between fasting and after intake of rice gruel in both the 0%G and 0.8%G groups. HTGL has been thought to play a role in remnant metabolism. A previous report showed no change in HTGL activity after an infusion of lipid emulsions [35]. Plasma HTGL remains in a fairly static equilibrium with the vascular binding site HTGL levels, and that shifts in metabolic conditions do not rapidly change either HTGL activity or its interaction with these vascular sites [17]. In the present study, circulating levels of FFA decreased continuously; therefore, local FFA concentrations near the HTGL binding site might not have increased.

This study had some limitations. First, we only examined a small number of subjects. In addition, this study did not assess the levels of other TG-related markers (e.g., chylomicron) or activity of LPL. Thus, the current study is only preliminary, and its limitations should be addressed in future.

Conclusions

In conclusion, our study results demonstrated a novel pleiotropic effect of KGM. Supplementation of KGM powder in rice gruel sustained lower levels of triglycerides accompanying elevation of LPL and GPIHBP1, which attenuated lipid metabolism. Further study is needed to elucidate the regulatory mechanism underlying reduction of triglycerides and elevation of LPL/GPIHBP1 induced by KGM supplementation.

Abbreviations

BMI: Body mass index; ELISA: Enzyme-linked immunosorbent assay; GPIHBP1: Glycosylphosphatidylinositol anchored high-density lipoprotein binding protein 1; HDL-C: High-density lipoprotein cholesterol; HTGL: Hepatic triglyceride lipase; KGM: konjac glucomannan; LDL-C: Low-density lipoprotein-cholesterol; LPL: Lipoprotein lipase; RLP-C: Remnant-like particles-cholesterol; sdLDLC: Small dense low-density lipoprotein-cholesterol; TC: Total cholesterol; TG: Triglyceride; TRLs: triglyceride-rich lipoproteins; VLDL: very low-density lipoprotein; 0%G: konjac glucomannan-free rice gruel; 0.4%G: rice gruel containing 0.4% konjac glucomannan powder ; 0.8%G: rice gruel containing 0.8% konjac glucomannan powder; 75gOGTT: 75g oral glucose tolerance test.

Declarations

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Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. All data generated or analyzed during this study are included in this published article.

Authors' Contributions

Conceptualization: AY, TK, and MM. Data curation: AK, TK, and KT. Formal analysis: AK, TK, and KT. Funding acquisition: AY, KT, TK, and MM. Investigation: AY, TK, KT, OA, KU, HI, YS, and SH. Methodology: AY, TK, KT, OA, KU, HI, YS, and SH. Supervision: MM. Validation and visualization: AY, TK, KT, OA, KU, HI, YS, and SH. Drafting and writing of the original article: AY, TK, and MM. Writing – review and editing: TK and MM. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All participants provided informed consent, and the Gunma University Ethics Review Board for Medical Research Involving Human Subjects approved the study protocol (UMIN registration number: UMIN000025950, registered at February 1st. 2017; https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000029247) according to the Helsinki Declaration.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

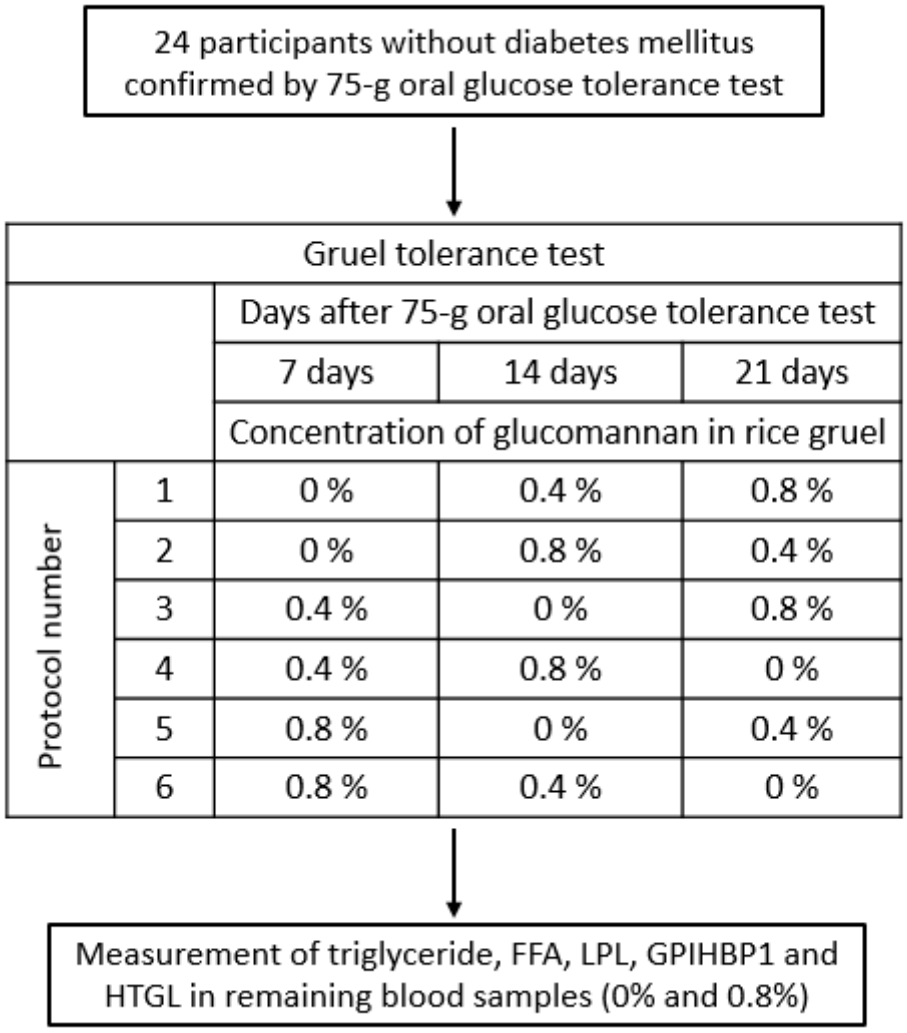

Figure 1

Study design. Twenty-four participants without past history of diabetes mellitus received gruel tolerance test. All 24 participants ingested three concentrations of KGM (0%, 0.4%, and 0.8%) in rice gruel within 3 weeks.

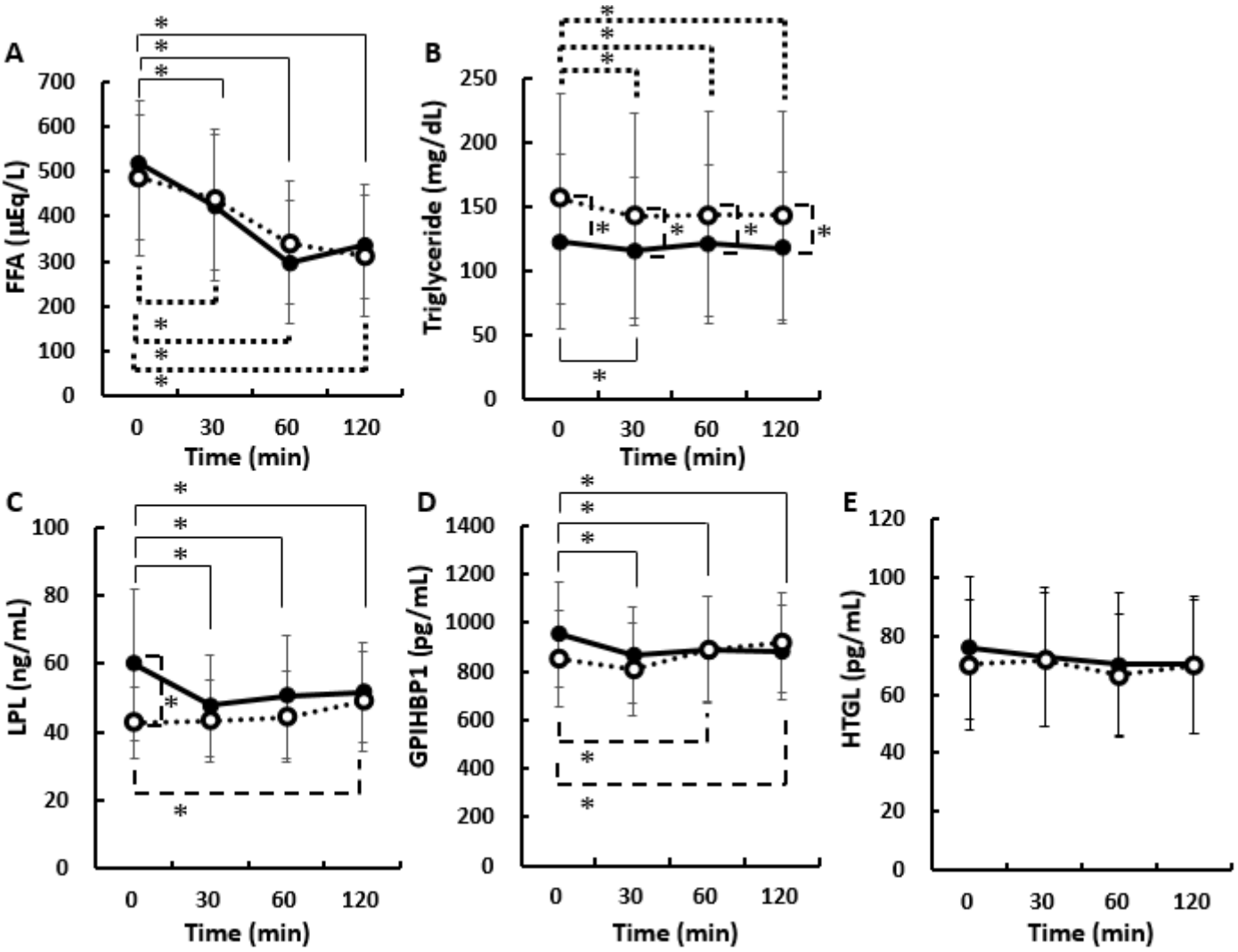

Figure 2

Sequential changes in serum FFA (A), triglycerides (B), LPL (C), GPIHBP1 (D), and HTGL (E) during the gruel tolerance test. KGM concentrations were 0% (closed circle) and 0.8% (open circle) during the rice gruel tolerance test. n = 24. Data are presented as means ± SDs. $p < 0.05$

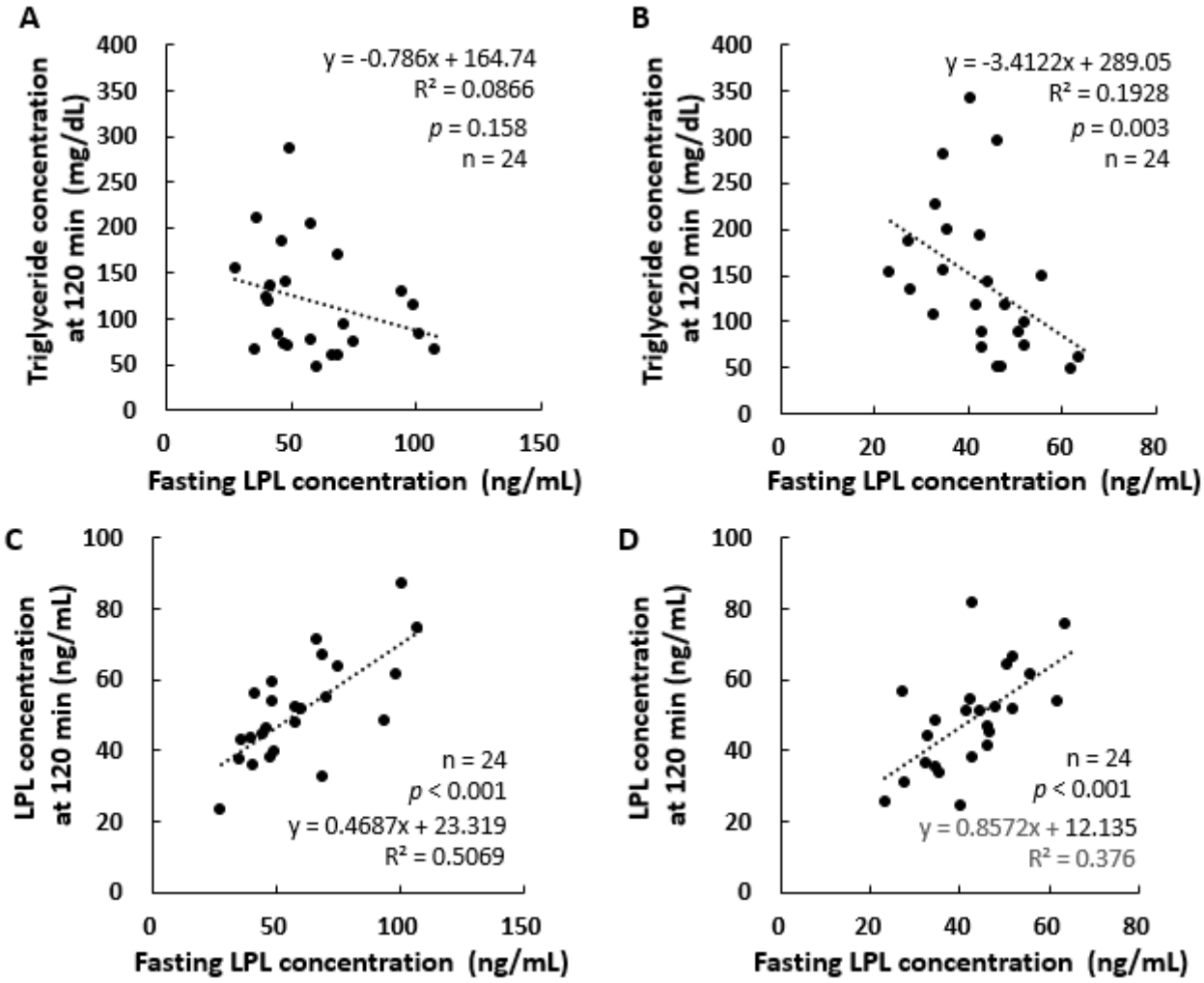

Figure 3

Relationship between serum fasting LPL concentration and triglycerides concentration at 120 min in the 0%G group (A) or 0.8%G group (B) among the 24 participants. Relationship between serum fasting LPL concentration and LPL concentration at 120 min in the 0%G group (C) or 0.8%G group (D) among the 24 participants.