Research Square

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Baseline Insulin Levels may Predict Response to Low Glycemic Index Complete Nutrition Formula: A Randomized Cross-Over Control Trial

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Abstract

Background: Personalized intervention is crucial for effective nutritional advice to prevent diabetes. However, specific characters of the responders to low glycemic index (low GI) diet was unclear. This study was aimed to identify glycemic index and factors affecting response to the low glycemic complete nutrition formula.

Method: A randomized cross-over controlled trial was conducted in 18 healthy volunteers (fasting plasma glucose < 100 mg/dL). All participants consumed complete nutrition drink with retrograded starch, glucose solution and white bread (35 g carbohydrate each) in a random sequence with 14-day wash-out intervals. The GI value of complete nutrition drink was determined from area under the curve (AUCi) of postprandial glucose, using glucose solution and white bread as references. Baseline characters of responders (with low GI of complete nutrition drink) and non-responders were compared and correlated to identify factors affecting their responses to the low GI complete nutrition drink.

Results: The adjusted GIs for complete nutrition drink with retrograded starch were 48.2 ± 10.4 and 46.7 ± 12.7 when using glucose solution and white bread as the reference food, respectively. Baseline insulin level was the only parameter showing difference between responders and non-responders. The response correlated with baseline insulin ($r = 0.4997$, $p = 0.0347$), but was independent of fasting plasma glucose ($r = 0.0456$, $p = 0.8574$) and others.

Conclusions: In healthy volunteers with normal blood glucose levels, adequate baseline insulin level was the only factor correlated with the response to low glycemic complete nutrition drink. Screening for fasting insulin level may be encouraged for personalized nutrition of low GI diet.

Trial registration: TCTR, TCTR20210305001. Registered 4 March 2021 - Retrospectively registered, http://www.thaiclinicaltrials.org/ TCTR20210305001

1. Introduction

Hyperglycemia, or high blood glucose level, is usually caused by the inability of cells to fully respond to insulin [1]. Diet management plays a key role in both diabetes prevention in healthy people and glycemic control in diabetic patients [2]. Previous studies showed that glycemic index is the strongest predictor of glycemic response [3].Consumption of food with high glycemic index may increase risk of hyperglycemia and insulin resistance [4].

Glycemic index (GI) has been used to identify different sources of carbohydrates, which affect post-meal glycaemia [4]. According to recommendation, foods with GI values of less than 55, 55–70 and more than 70 are classified as low-GI, medium-GI and high-GI, respectively [5]. A previous study showed that bean puree (low GI starch) induced lower glycemic response than that of potato (high GI starch) [6]. A study in obese pubertal boys reported that low GI food enhanced satiety and lower voluntary intake [7].

Importantly, many studies suggested that low GI diet helped control blood sugar and reduced risk of Type II DM [8–10].

Dietary factors, low-GI diet, are known to play a role in diabetic prevention. However, one intervention may not be proper for all population. A previous study in 900 people showed that different people have tremendously varied glycemic response to the same meal [11]. Therefore, generalized dietary recommendations may actually have an impact only on specific group of population. Scientific data are required to predict the target group suitable for a specific intervention. Appropriate personalized intervention is essential for providing nutritional advice to prevent diabetes.

Personalized nutrition is based on the concept that one size does not fit everyone. Differences in biochemical, metabolic, genetic, microbiota and other factors contribute to the huge inter-individual differences observed in response to nutrition intervention [12].

However, the information about specific background characters of responders to low-GI diet is scarce. A complete nutrition formula aiming to reduce GI value was formulated with retrograded starch and other basic nutrients. This randomized control trial was aimed to identify glycemic index and factors affecting glycemic response to the low glycemic complete nutrition formula.

2. Materials And Methods

2.1 Ethical aspects and setting

The protocol MU-CIRB 2018/148.2007 was approved by the Mahidol University Central Institutional Review Board (MU-CIRB) with the COA. No. MU-CIRB 2018/163.1109. This research was performed according to International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice (ICH-GCP) and Declaration of Helsinki. The informed written consent was obtained from each participant before the study. The protocol was registered in Thai Clinical Trial Registry (TCTR20210305001). The protocol of Thai clinical trials registry can be accessed at http://www.thaiclinicaltrials.org/TCTR20210305001

2.2 Study design, blinding, random allocation and concealment

A randomized-crossover controlled trial was used. Participants who qualified screening were randomly assigned into three groups with equal allocation ratio. Minimization was applied to ensure that all groups are matched for sex, age, body mass index (BMI) and biochemical data. Each group received a different sequence of test foods, i.e. complete nutrition drink, glucose solution and white bread (Table 1). A researcher performed random allocation. Sample collector and laboratory analyzers were blinded from the test food until the end of the study.

2.3. Participants

The inclusion criteria for screening participants were healthy people aged more than 18 years old who had body mass index less than 30 kg/m^2, no systematic diseases and normal blood biochemical parameters (complete blood count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, blood urea nitrogen (BUN), creatinine, cholesterol, high density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides and fasting plasma glucose (FPG) (< 100 mg/dL. The exclusion criteria of participants included alcoholism, cigarette smoking, pregnancy, dairy or gluten allergy, under medical therapies and unable to maintain regular physical activity throughout the study. All participants signed their informed written consent before data collection.

2.4. Sample size

Previous studies utilized 15 participants for glycemic index identification of starchy food [13]. However, this study required three visits of data collection and each visit required multiple venous blood collections. Considering expected withdrawal of the participants, 20% drop-out, sample size was set at eighteen participants (n = 18).

2.5. Intervention and materials

All participants consumed 250 mL of complete nutrition drink, 75 g of white bread, and 250 mL of glucose solution in a random sequence. Each test food contained 35 g of available carbohydrate equally as recommended (25–50 g of available carbohydrate [4]). Since complete nutrition drink has thick liquid consistency, we utilized both white bread and glucose solution as the reference foods [14]. Complete nutrition drink was made by dissolving the powder in warm water (around 65°C). The powder was made from retrograded starch and other nutrients. It was manufactured by Chiangmai Bioveggie Co., Ltd. White bread was made from wheat flour, sucrose, vegetable fat, yeast, blends, milk powder, and iodized salt. White bread was a product of President Bakery Public Company, Ltd. (Bangkok, Thailand). Glucose solution was made by dissolving 35 g glucose powder (Utopian, Co., Ltd., Thailand) in 250 mL of drinking water. Table 2 shows nutrient contents of 250 mL of complete nutrition drink, 35 g of glucose solution and 75 g of white bread. All of these food items had an equal amount of digestible carbohydrate.

2.6. Study procedure

The study was conducted at Institute of Nutrition, Mahidol University. Participants who passed the screening were randomly assigned into three groups. All participants consumed all test foods in random sequence. The first, second and third groups were started with complete nutrition drink, glucose solution and white bread, respectively. Each intervention was separated by 14 days wash-out periods. After overnight fasting, participants consumed each food within five minutes. They were instructed to sit comfortably. Blood samples were collected at fasting (before food intake), 0, 15, 30, 45, 60, 90, 120, 150 and 180 minutes after finished the food for determining plasma glucose level [15]. Plasma insulin was measured at 0 min (baseline) and postprandial intervals of 30, 45, 60, 90, 120, 150 and 180 minutes.

2.7. Monitoring

The habitual diet and physical activity were assessed by using dietary record and international physical activity questionnaire (IPAQ) during wash-out periods [16]. In each washout period, all participants were asked to do 3-day food records weekly which included two weekdays and one weekend day. Energy and dietary intake was analyzed by using the INMUCAL-Nutrient V. 3.2 program [16]. Habitual physical activity was divided into low, medium and high levels according to their total MET-minute-week of physical activities [17–18]. Before the test day, participants were asked to refrain from food for 12–15 hours. Sipping water was allowed. All participants consume similar last evening meals (rice with stir fried vegetables and meat) before all test days [19]. Furthermore, all participants were asked to avoid heavy exercise, abstaining from heavy meals at least 24 hours before test time, abstaining from alcoholic beverages and smoking throughout the study [16].

2.8. Clinical outcome measurement

The primary outcome measures were postprandial glucose response and glycemic index of complete nutrition drink. The plasma glucose level was measured by an enzymatic hexokinase method [16] using Layto RT9200 (Rayto Life and Analytical Sciences Co.,Ltd., Shenzhen, P.R.China). A line graph between plasma glucose concentration and time was generated for each participant for each test food. AUC_i of glucose for each test food were calculated geometrically over a 3- hour period [3]. Only the values above fasting concentration were used to compute AUCi [20]. GI values were calculated by using both glucose and white bread as references. The following equation was used for calculation of GI using glucose as reference [4].

$$GI = \frac{glucose AUCi(0-3h)(test\ food)}{glucose AUCi(0-3h)(glucose)} x\ 100$$

The average glycemic index of white bread was 71.2, compared to 100 for glucose solution. Thus, when using white bread as reference, the GI must be divided by 1.4 as following [15, 21].

$$GI = (\frac{glucose AUCi\ (0-3h)(test\ food)}{glucose AUCi\ (0-3h)(white\ bread)} x\ 100)/1.4$$

The secondary outcome measure was plasma insulin response. Plasma insulin concentration was measured by electrochemiluminescence immunoassay (ECLIA) [22] using cobas® 8000 modular analyzer series (Roche Roche Diagnostics International AG, Rotkreuz, Switzerland). A line graph between plasma insulin concentration and time was generated for each participant for each test food. AUC_i of insulin for each test food were calculated geometrically over a 3- hour period.

2.9. Statistics

The baseline numerical characteristics of participants were displayed using mean and standard deviation (SD). Statistical tests were selected based on the normality of data. Normality tests were performed for all data by using Shapiro-Wilk test. Comparison of baseline characteristics among three randomized groups were analyzed by one-way ANOVA for normal distributed data or Kruskal-Wallis test for skewed

distributed data. The average plasma glucose levels at each time point were compared among different foods by using Repeated measures ANOVA followed by Tukey's tests. Baseline glucose levels and AUCi of glucose or insulin were compared among different test foods by using Friedman test followed by Dunn's test. Correlations between various factors and response to low glycemic complete nutrition drink were analyzed by using Spearman rank correlation analysis. Physical activity levels and dietary intakes were compared between the two washout periods by using Chi-square test and Wilcoxon signed rank test, respectively. All statistical tests were performed by using two-tailed test. Bonferroni correction was applied if multiple comparisons are performed. P-value < 0.05 was considered statistically significant. Graph Pad Prism V.9.0.2 was used for graphing and statistical analysis.

3. Results

Participant flow chart

This study was conducted during September- December, 2020. **Figure.1** shows Consolidated Standards of Reporting Trials (CONSORT) diagram. Thirty-three volunteers were recruited to the study. After screened, fifteen subjects were excluded. Eighteen participants including nine males and nine females (22 – 48 years) were randomly assigned into three groups. All participants completed all tests; thus, the data was intention-to-treat analyzed from all randomized participants.

Baseline characteristics

As shown in **Table S1** (Supplemental material), all average baseline laboratory parameters, except for total cholesterol, were in normal range. Although the mean of total cholesterol was higher than the normal range, the means of total cholesterol to HDL-C ratios were normal (less than 5.0 for male and less than 4.5 for female [23]). **Table 3** shows no statistically significant differences in age, BMI and laboratory characteristics among the randomized groups (p-value ≥ 0.05).

Postprandial glucose response

Figure 2a shows no significant difference of fasting plasma glucose levels among all test days. After consuming the complete nutrition drink, the postprandial glucose concentrations were rapidly risen and peaked at 20 min. In contrast, those of glucose solution and white bread reached maximum levels at 35 and 50 min, respectively (**Figure 2b**). While the plasma glucose levels of complete nutrition drink were declined first, those of glucose solution and white bread continuously remained high. **Table 4** shows that the average AUCi of glucose response for complete nutrition drink (mean ± SE: 1,574 ± 378.0, 95% CI: 833.5, 2420) was significantly lower than those of glucose solution (p = 0.0026, mean ± SE: 3,612 ± 577.9, 95% CI: 2393, 4831) and white bread (p= 0.0001; mean ± SE: 2,974±448.6, 95% CI: 2028, 3921). The effect size was 7.04 and 7.11 for comparison with glucose solution and white bread, respectively. The average GI of complete nutrition drink were 48.2 ± 10.4 when using glucose solution as reference food, which was not statistically different from the GI calculated when using white bread as the reference food (46.7 ± 12.7; p > 0.99).

Postprandial insulin response

Figure 2c shows that after consuming complete nutrition drink the postprandial insulin concentrations were risen and peaked at 50 min, while the highest peak for glucose solution and white bread were at 50 and 35 min, respectively. The plasma insulin response of complete nutrition drink was continuously remained higher than baseline throughout the 3-h period. In contrast, the insulin response to glucose solution and white bread were rapidly declined. Nevertheless, there were no statistically significant differences among groups. **Table S2** shows that the average AUCi of insulin response for complete nutrition drink (mean ± SE: 6317±1788, 95% CI: 2544, 10089) was higher than that of glucose solution (mean ± SE: 5710±1880, 95% CI: 1743, 9677) but lower than that of white bread (mean ± SE: 11378±4690, 95% CI: 1483, 21274). However, no statistically significant differences were observed among groups. The average maximum insulin concentrations of complete nutrition drink, white bread, and glucose solution were 96.19, 123.51, and 69.5 uIU/ mL, respectively.

Responders VS non-responders

Responders were the subjects showing low glycemic index of the complete nutrition drink, while the non-responders showed medium or high glycemic index. **Table 5** showed the list of responders and non-responders of complete nutrition drink. Responders were distributed in all three randomized groups suggesting that the sequence of intervention did not affect the response.

With regard to the factors affecting response to the low GI complete nutrition drink, baseline characteristics and dietary intakes were compared between responder and non-responder groups. Low-GI response correlated with only baseline insulin ($r = 0.4997$, $p = 0.0347$), but was independent of fasting plasma glucose ($r = 0.0456$, $p = 0.8574$) (**Table 6**). The correlation coefficients of the other variables are listed in **Table 6**. Interestingly, baseline plasma insulin level was the only parameter showing difference between groups. The average baseline insulin levels (mean ± SE) in the responder group was 14.86 ± 4.77 μIU/mL (95% CI: 4.36-25.35), which was significantly higher than that of the non-responder group (p-value = 04, mean ± SE: 4.89 ± 1.39 μIU/mL; 95% CI: 1.3 – 8.48). The effect size was 2.7. In contrast, there were no statistically significance differences for other factors including fiber intake, protein intake, age, HbA1C, BMI and HDL-C ratio, between responders and non-responder groups (**Figure 3**).

Dietary intake and physical activity

Figure 4 showed that there were no statistically significant differences of energy, protein dietary intake and percentage of energy distribution from carbohydrate, and physical activity levels between two washout periods (P-value ≥ 0.05).

Adverse events

Throughout the entire study, there were no adverse events occurring with any participants.

4. Discussion

A previous study presented the data of 900 people, they showed that different people have tremendously different responses to the same meal [11]. However, there are lacking of the information about specific background characters of responders to low-GI diet. The GI values acquired from the present study were 48 (calculated with glucose solution as reference) and 47 (calculated with white bread as reference). Based on this information, the complete nutrition drink was classified as a low-GI food [5]. Baseline characteristics, dietary intake and habitual physical activity were accounted for the factor which may relate to the response. Interestingly, in this present study the baseline insulin was the only factor affecting the response between responders and non-responders. Such finding suggested that the response to low-GI complete nutrition drink depends on baseline insulin. Two components influencing *in vivo* insulin secretion include basal insulin at fasting state and the effect from meal [24]. The average baseline insulin of non-responder group was 4.89 ± 3.4, while normal range of baseline insulin for healthy population is between 5 and 15 uIU/mL [25]. Therefore, the baseline insulin of non-responder group in this study was slightly lower than normal reference range. Interestingly, insufficiency of available plasma insulin was shown to link with defects in cellular glucose uptake [26]. For this reason, it is possible that lower insulin concentration at fasting state in non-responder group may contribute to higher AUC_i of plasma glucose when test food was ingested. Based on the findings of this study, individuals with adequate baseline insulin level could be the target group of the complete nutrition drink. A future large-scale study is warranted to confirm such hypothesis.

Moreover, personalized nutrition is an approach to provide dietary interventions to the right person based on individual background [27]. Identification of specific target group likely respond to the intervention is the key. A previous study reported high inter-individual variability in postprandial lipemic responses. There are a great differences in magnitude and pattern of lipemic response to the same meal in healthy participants [28]. In the same way, another research showed that insulin resistance (differ type) have positive response to the different diet type. Mediterranean diet was more likely to have positive effect on individuals with a muscle insulin resistance, whereas individuals with liver insulin resistance were more likely to have positive effect from the low-fat diet [29]. To summarize, personalized nutritional recommendation could essential to improving nutritional status in healthy populations. A further studies about the association between baseline characteristic including blood parameters, anthropometrics, gut microbiome, dietary behavior, etc. and low-GI formula are required to confirm such hypothesis.

In addition, the underlying mechanism behind such low GI value of the complete nutrition drink was likely derived from retrograded rice flour. Retrogradation of starch was shown to increase slowly digestible fractions of carbohydrate [12, 14]. Such action could reduce postprandial glucose response [14–15]. Besides retrograded starch, complete nutrition drink also contains 19% protein and 22% fat which could increase insulin production and slow down glucose absorption [31–32]. Such mechanism could also contribute to the low GI nature of the complete nutrition drink. In fact, after consuming complete nutrition drink the peak and AUCi of insulin response were higher than those of glucose solution, although the difference was not statistically significant. Previous study estimated that variability in insulin responses

was derived from glycemic response (23%) and macronutrient content (10%) [33]. Therefore, both retrograded starch, protein and fat contents may contribute to the differential insulin response of the complete nutrition drink.

The strength of this study was the design of randomized cross-over controlled trial. The sequence of interventions were randomly assigned for match groups. And all participants served as their own controls. Such design helps reduce biases from individual metabolisms and residual effects from previous interventions. However, there were some limitations of this study. First, this study recruited any healthy volunteers regardless of physical activity levels. Therefore, their baseline physical activity were varied from low to high resulting in a great variation in glucose and insulin response among participants. Future research should select participants with similar levels of physical activity. Last, the present study focused on an acute effect of complete nutrition drink on postprandial glucose response. Thus, whether baseline insulin could affect long-term response to complete nutrition drink remains to be elucidated. Based on the low GI of complete nutrition drink, it will be worthwhile to further investigate its long-term effects on blood glucose control in diabetic patients.

5. Conclusion

The findings of this pilot study suggested that adequate baseline insulin level was the only factor correlated with the response to low glycemic complete nutrition drink. Future large-scale research is warranted to confirm the role of baseline insulin on individual response to low glycemic diet. Then, screening for fasting insulin level may be encouraged for personalized nutrition of low GI diet.

Declarations

Ethics approval and consent to participate: MU-CIRB 2018/148.2007 was approved by the Mahidol University Central Institutional Review Board (MU-CIRB) with the COA. No. MU-CIRB 2018/163.1109. All study participants, or their legal guardian, have provided informed written consent before the enrollment.

Consent for publication: Not applicable

Availability of data and materials: The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Clinical trial registration statement: This study is registered at Thai Clinical Trial Registry. The registration identification number is TCTR20210305001).

Competing interests: TW received a financial and product support for this research from the Chiangmai Bioveggie, Co. Ltd. No competing financial interest exists for other authors. The authors have full control of all primary data and agreed to allow the journal to review their data if requested.

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Authors' contributions: WW designed, collected, analyzed and interpreted data, and drafted the manuscript; NR and NM collected data; TW obtained funding, designed and edited manuscript; DT obtained ethical approval of the project, designed, performed randomization, supervised clinical trial operation, interpreted data and edited the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1: The sequence of interventions in each randomly organized group

No.	Matching parameters	Food sequence		
		Session 1	Session 2	Session 3
Group 1 (n = 6)	Gender, age, BMI, Biochemical data	Complete nutrition drink	White bread	Glucose solution
Group 2 (n = 6)	Gender, age, BMI, Biochemical data	Glucose solution	Complete nutrition drink	White bread
Group 3 (n = 6)	Gender, age, BMI, Biochemical data	White bread	Glucose solution	Complete nutrition drink

Table 2: Nutrient contents of complete nutrition drink (250 mL), glucose solution (35 g) and white bread (75 g)

	Complete nutrition drink	Glucose solution	White bread
Total energy (kcal)	280	140	203
Energy from fat (kcal)	60	0	31.3
Total fat (g)	7	ND	3.9
Saturated fat (g)	4	ND	2.3
Cholesterol (mg)	20	ND	ND
Protein (g)	13	ND	7.8
Total carbohydrate (g)	41	35	35
Digestible carbohydrate (g)	36	35	33
Dietary fiber (g)	5	ND	2
Sugar (g)	6	35	4.7
Vitamin B-1 (mg)	0.68	ND	0.1
Vitamin B-2 (mg)	0.99	ND	0.1
Vitamin B-6 (mg)	0.91	ND	ND
Vitamin B-12 (μg)	2.74	ND	ND
Sodium (mg)	310	ND	343.7
Calcium (mg)	679	ND	25
Iron (mg)	4.71	ND	0.5

ND: not detectable

Table 3: Demographic characteristic of randomized groups

Characteristics	Group 1 (n = 6)	Group 2 (n = 6)	Group 3 (n = 6)	P-value
Sociodemographic data				
Male: Female (n)	3: 3	3: 3	3: 3	
Age (years)[a]	30.8 ± 8.93	33.5 ± 7.34	31 ± 9.03	0.83 [b]
Anthropometry data [a]				
BMI, kg/m^2	21.2 ± 2	21.4 ± 2.57	20.8 ± 2.22	0.89 [b]
Biochemical data [a]				
Fasting plasma glucose, mg/dL	93.5 ± 6.38	98.2 ± 6.59	94 ± 4.47	0.52 [c]
HbA1c, %	5.13 ± 0.43	5.22 ± 0.53	5.25 ± 0.29	0.89 [b]
BUN, mg/dL	11.7 ± 3.56	11 ± 3.16	10.8 ± 2.48	0.95 [c]
Creatinine, mg/dL	0.77 ± 0.08	0.77 ± 0.23	0.78 ± 0.08	0.67 [c]
Total cholesterol, mg/dL	224 ± 35.1	211 ± 23.8	229 ± 36.4	0.59 [b]
Triglyceride, mg/dL	103 ± 43.5	105 ± 30.4	87.2 ± 13.2	0.59 [b]
HDL-C, mg/dL	64.7 ± 16.7	59.3 ± 11.8	64.3 ± 10	0.74 [b]
LDL-C, mg/dL	138 ± 34.7	131 ± 23.2	147 ± 30.8	0.63 [b]
Total cholesterol: HDL-C ratio	3.27 ± 0.73	3.3 ± 0.71	3.32 ± 0.57	0.99
AST, U/L	14.8 ± 5.42	13.5 ± 4.64	10.7 ± 2.58	0.27 [b]
ALT, U/L	17.5 ± 10	18.2 ± 10	15.3 ± 5.96	0.85 [b]
Total bilirubin, mg/dL	0.62 ± 0.21	0.55 ± 0.14	0.53 ± 0.29	0.79 [b]

[a] Values of the parameters were mean ± SD; P-values were from [b] One-way ANOVA, [c] Kruskal-Wallis test; BMI: Body mass index; FPG: Fasting plasma glucose; HDL-C: High density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; BUN: Blood urea nitrogen; AST: Aspartate transaminase; ALT: Alanine transaminase; U/L: unit per liter

Table 4: Individual and average area under curve incremental (AUCi) of postprandial glucose response and glycemic index (GI) values of complete nutrition drink

Subject code	AUCi CND [a]	AUCi Bread	AUCi GS [b]	GI CND/Bread [c]	GI CND/GS [d]
1a	1,168.0	1,725.0	5,357.0	48	22
1b	303.1	2,028.0	3,182.0	11	10
1c	4,151.0	1,238.0	4,641.0	239	89
1d	842.5	4,485.0	891.9	13	94
1e	222.0	2,340.0	1,469.0	7	15
1f	1,836.0	6,174.0	6,474.0	21	28
2a	2,465.0	2,112.0	8,529.0	83	29
2b	2,264.0	2,745.0	4,350.0	59	52
2c	131.1	174.9	1,368.0	54	10
2d	5,679.0	5,734.0	6,779.0	71	84
2e	4,103.0	7,436.0	2,286.0	39	179
2f	156.8	3,744.0	865.9	3	18
3a	1,096.0	1,968.0	1,510.0	40	73
3b	189.8	3,115.0	2,537.0	4	7
3c	1,146.0	1,388.0	2,670.0	59	43
3d	622.4	3,474.0	905.7	13	69
3e	526.4	1,769.0	7,465.0	21	7
3f	1,436.0	1,888.0	3,734.0	54	38
Mean ± SE	**1,574 ± 378**	**2,974 ± 449****	**3,612 ± 578********	**46.7 ± 12.7**	**48.2 ± 10.4** [d]

[a] AUCi CND: area under curve incremental of glucose and time after consuming complete nutrition drink; [b] AUCi GS: area under curve incremental of glucose and time after consuming glucose solution; [c] GI CND/ Bread: glycemic index calculated from the ratios of AUCi between that of complete nutrition drink and bread divided by conversion factor of 1.4; [d] GI CND/ GS: glycemic index calculated from the ratios of AUCi between that of complete nutrition drink and glucose solution; (**) means $p < 0.01$, (****) means $p < 0.0001$, compared with that of complete nutrition drink, Friedman test followed by Dunn's multiple comparison test; [d] $p > 0.99$ for comparison of glycemic index, Wilcoxon matched-pairs signed rank test

Table 5: The list of responders for complete nutrition drink

	Glucose solution		White bread	
	responder (n=12)	non-responder (n=6)	responder (n=13)	non-responder (n=5)
subject code	1a	1c	1a	1c
	1b	1d	1b	2a
	1e	2d	1d	2b
	1f	2e	1e	2d
	2a	3a	1f	3c
	2b	3d	2c	
	2c		2e	
	2f		2f	
	3b		3a	
	3c		3b	
	3e		3d	
	3f		3e	
			3f	

The table lists codes of participants who showed low glycemic index of complete nutrition drink (responder), compared to glucose solution or white bread as specified. The code 1, 2, 3 represents the randomized group 1, 2, 3 who received all interventions in different sequences.

Table 6: Spearman's rank correlation coefficient between baseline characteristics, dietary intake, physical activity and various factors

Variable	Correlation coefficient (r)	95% CI	P value	P value summary
Sex	0.24	-0.2736 to 0.6418	0.3464	ns
Age (year)	0.00	-0.4785 to 0.4785	>0.9999	ns
BMI (kg/m^2)	-0.23	-0.6365 to 0.2820	0.3647	ns
Baseline insulin (ulU/mL)	0.50	0.02793 to 0.7895	0.0347	*
Baseline glucose (mg/dL)	0.05	-0.4425 to 0.5129	0.8574	ns
BUN (mg/dL)	-0.29	-0.6739 to 0.2205	0.2457	ns
Creatinine (mg/dL)	-0.46	-0.7706 to 0.02026	0.0532	ns
eGFR (ml/min/1.73m^2)	0.34	-0.1640 to 0.7047	0.1658	ns
Cholesteral (mg/dL)	-0.02	-0.4958 to 0.4608	0.9287	ns
Triglyceride (mg/dL)	-0.03	-0.5044 to 0.4518	0.8931	ns
HDL (mg/dL)	0.24	-0.2702 to 0.6440	0.339	ns
LDL (mg/dL)	-0.05	-0.5128 to 0.4427	0.8579	ns
HDL ratio	-0.10	-0.5537 to 0.3956	0.6863	ns
AST (U/L)	0.06	-0.4332 to 0.5213	0.822	ns
ALT (U/L)	-0.08	-0.5377 to 0.4146	0.7533	ns
Total bilirubin (mg/dL)	-0.40	-0.7400 to 0.09127	0.0956	ns
Dietary intake				
Energy (kcal)	0.34	-0.1646 to 0.7044	0.1665	ns
Fiber (g)	0.05	-0.4422 to 0.5132	0.8559	ns
Sugar (g)	0.20	-0.3036 to 0.6222	0.4153	ns
CHO distribution (%)	0.07	-0.4238 to 0.5297	0.7868	ns
PRO distribution (%)	0.24	-0.2682 to 0.6453	0.3348	ns
Fat distribution (%)	-0.28	-0.6666 to 0.2331	0.2673	ns
IPAQ score	0.16	-0.3458 to 0.5924	0.5286	ns

CI, confidence interval; ns, not statistically significant. Table reports the Spearman's rank coefficient correlation (r) for the relationship between each personal factors and low-GI response analyzed by nonparametric Spearman correlation. Dummy code for outcome (low-GI response): 0 = negative, 1 = positive. *$P < 0.05$

Figures

Figure 1. The diagram depicts number of recruited volunteer and actual number of participants included in data analysis.

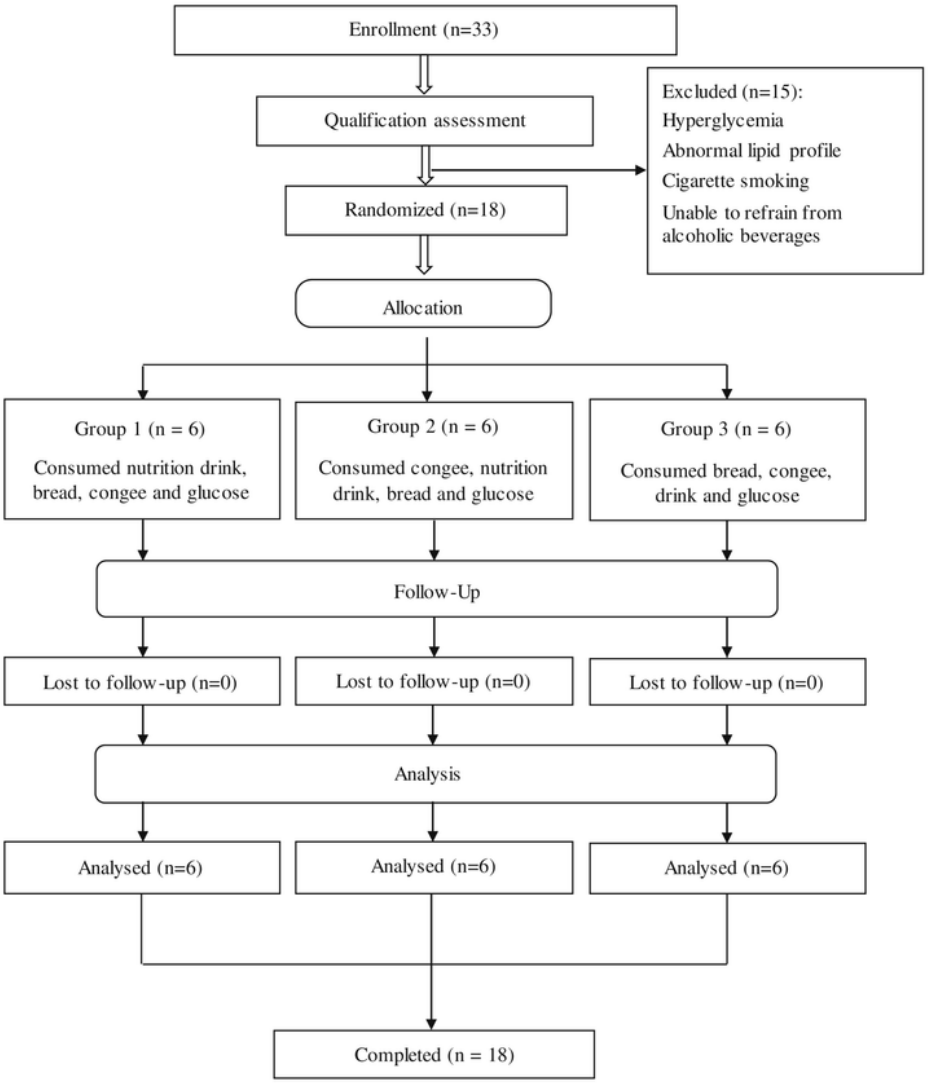

Figure 1

CONSORT participants' flow chart

Figure 2

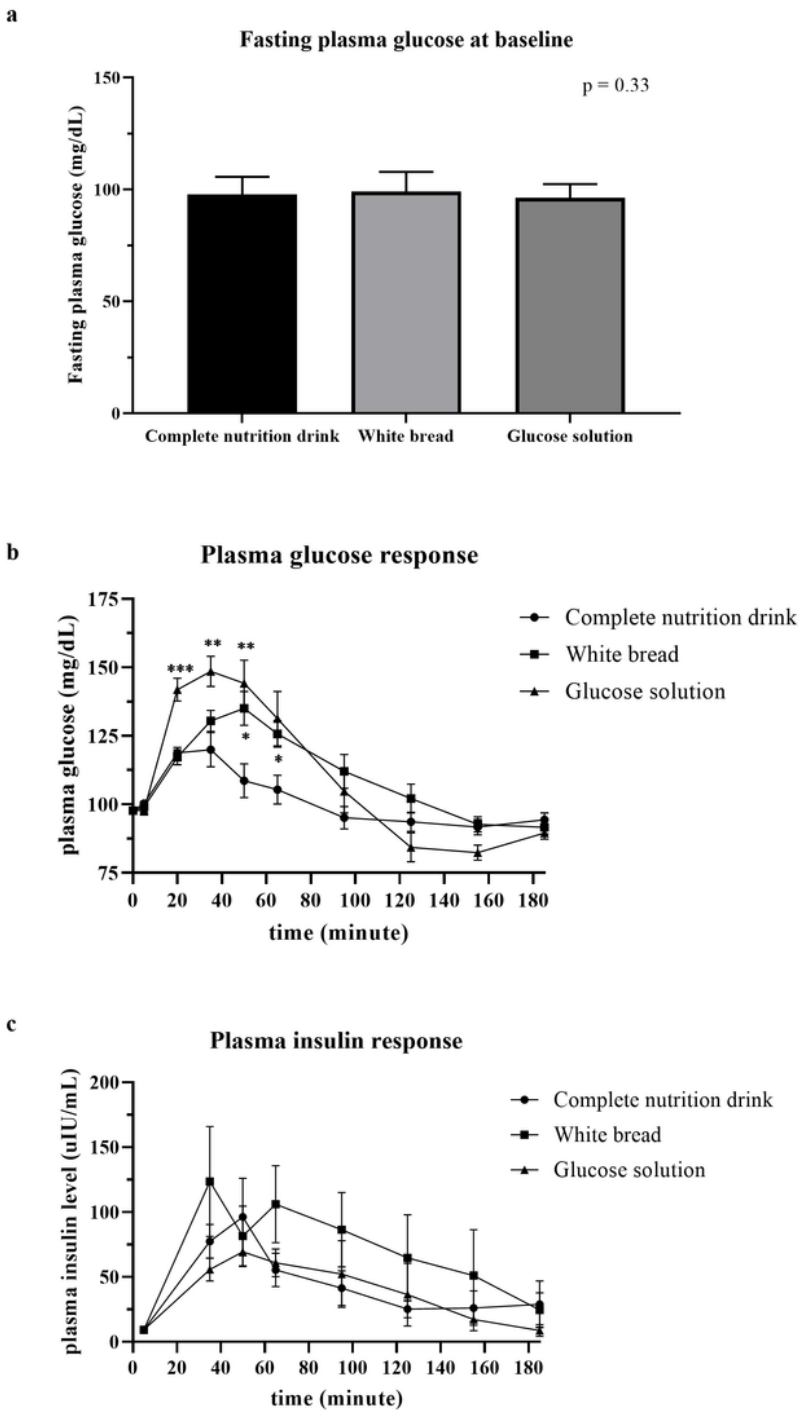

Figure 2

Postprandial glucose and insulin response after test food consumption a: Bar graph showed mean ± SEM of plasma glucose concentration (mg/dL) in all participants (n=18) at baseline before complete

nutrition drink, white bread and glucose solution consumption as specified. The p-value was from Friedman test. b: Mean ± SEM of plasma glucose concentration (mg/dL) in all participants (n=18) at 0, 5, 20, 35, 65, 95, 125, 155, 185 min of each test day, i.e. fasting (before food intake), 0, 15, 30, 60, 90, 120, 150, and 180 min, respectively after complete nutrition drink, white bread and glucose solution consumption as specified. (*) means p-value < 0.05, (**) means p-value < 0.01, (***) means p-value < 0.001, repeated measures Two-way ANOVA followed by Tukey's multiple comparison tests). c: Mean ± SE plasma insulin concentration (uIU/mL) in all participants (n=18) at 0, 30, 60, 90, 120, 150, and 180 after complete nutrition drink, white bread and glucose solution consumption as specified. P-value was obtained from repeated measures Two-way ANOVA.

Figure 3

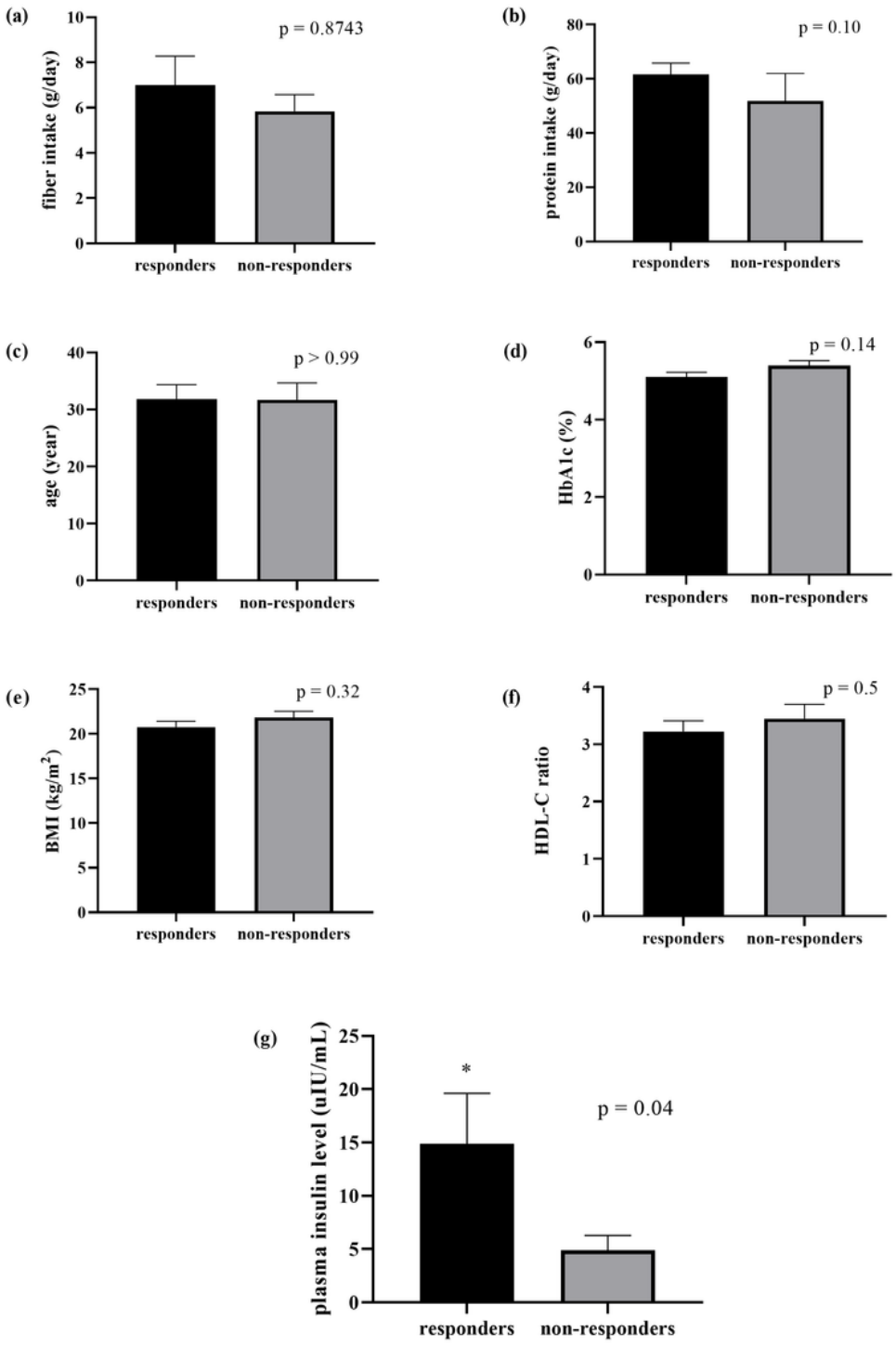

Figure 3

The comparison of baseline characteristics between responders and non-responders group, when using glucose solution as reference food Bar graph showed comparison of mean ± SE of fiber intake (a: g/day), protein intake (b: g/day), age (c: year), HbA1c (d: %), BMI (e: kg/m2), (e: g/day), HDL-C ratio (f), and baseline insulin (g: uIU/mL) of responder and non-responder groups. P-values were obtained from Mann-Whitney tests except HbA1C, BMI and HDL-C ratio which were from unpaired t-tests.

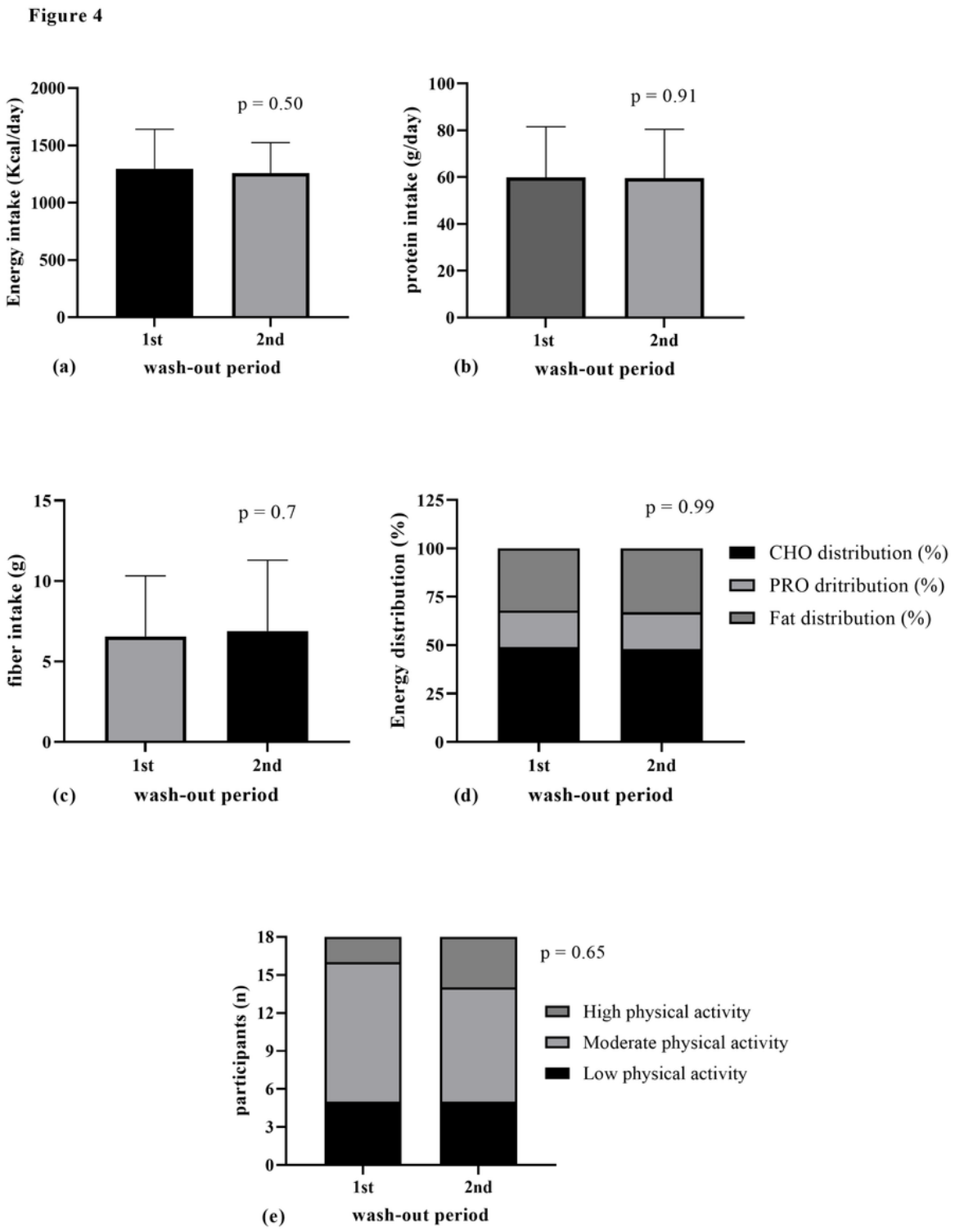

Figure 4

Monitoring of usual dietary intake and physical activity Bar graph showed comparison of mean ± SD of energy intake (kcal/day) (a), protein intake (g/day) (b), fiber intake (g/day) (c), and carbohydrate distribution (%) (d), between the 1st and 2nd washout periods, P-values were obtained from Wilcoxon signed rank test. (e): Stacked bar showed comparison of the number of participants with high, moderate,

and low habitual physical activity between the 1st and 2nd washout periods, P-values were obtained from Chi-square test.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementmaterials.docx