

A randomized controlled clinical trial of carbohydrate mix-fortified nutrition in type 2 diabetes mellitus patients

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ABSTRACT

BACKGROUND Liquid meal replacement nutrition (LMRN) contains low glycemic index food (isomaltulose, resistant dextrin, and inulin), which can decrease large blood glucose level fluctuations and reduce food intake. This study aimed to determine the stability of daily blood glucose and the level of appetite sensations after intake of LMRN in type 2 diabetes mellitus (DM) patients.

METHODS This randomized, controlled, crossover, and open-labeled study included 30 subjects with type 2 DM. Subjects attended two visit sessions to consume either LMRN or controlled-nutrition solid food (CNSF) for 4 consecutive days. Each subject had 2 days of 24-hour periods of blood glucose measurement using a continuous glucose monitoring system and had a 1-week washout period. Glycemic response (GR) and incremental area under the curve (iAUC) were calculated. The satiety level was measured using a visual analog scale.

RESULTS After 48 hours, LMRN reduced GR compared with CNSF with glucose measurements of 13.72 (30.42) and 17.47 (36.38) mg/dl, respectively. The reduction on iAUC after consuming LMRN (36,891 [30,255.8] mg.min/dl) compared with CNSF (40,641 [38,798.9] mg.min/dl) was also noted. Subjects having LMRN felt less hungry and more satiated than those consuming CNSF. The administration of LMRN does not have any serious side effects.

CONCLUSIONS LMRN provides a greater reduction of GR and longer term of satiety compared with CNSF without causing any serious side effects.

KEYWORDS liquid meal replacement nutrition, low glycemic index, type 2 diabetes mellitus

The Indonesian National Basic Health Research (*Riskesmas*) of the Ministry of Health reported that the prevalence of diabetes mellitus (DM) in 2018 is estimated at 10.9%.¹ According to the data of the International Diabetes Federation, there were over 10.3 million cases of diabetes in Indonesia in 2017.² Type 2 diabetes accounted for 90–95% of all diabetes cases. This form encompasses individuals who have a relative insulin deficiency and peripheral insulin

resistance. Complications of DM can be prevented by a good glycemic control, which is achieved with a balanced diet and nutrition therapy, physical activity, medication, and regular screening. Risks of type 2 DM have been associated with high saturated fat intake, high total fat intake, and inadequate fiber intake in the diet.³

The concept of glycemic index (GI) was introduced as classifying different sources of carbohydrate and

carbohydrate-rich food in the diet, depending on their effect on postprandial glycemia. GI is calculated from the incremental area under the postprandial plasma glucose curve of the food and, compared with that, following the consumption of 50 g carbohydrate from glucose or white bread, expressed as a percentage of the standard.^{4,5} GI can be classified into three categories, namely, low (≤ 55), medium (56–69), and high (≥ 70).⁶ Low GI food has clinical advantages in controlling glycemic response (GR) in DM patients.^{7,8} A low GI diet must be considered a part of the management strategy of diabetes.⁸

The liquid meal replacement nutrition (LMRN) used in this study contained carbohydrate mix-fortified (GI = 32), isomaltulose components (i.e., disaccharides including glucose and fructose), and resistant dextrin and inulin, which are polysaccharides that also serve as prebiotics.⁹ Isomaltulose is a slow and fully digestible carbohydrate and has low GI that provides sustained glucose release.

This study aimed to determine if a low GI diet for breakfast and mid-afternoon can affect the GR and satiety level of type 2 DM patients. This study had not been done yet. This study aimed to measure GR, incremental area under the curve (iAUC), and satiety level, and to identify the incidence of hypoglycemia and other adverse effects.

METHODS

This was a randomized, controlled, crossover, open-labeled study that aimed to compare the effect of carbohydrate mix-fortified LMRN on daily blood glucose levels of patients with type 2 DM within a 48-hour period with controlled-nutrition solid food (CNSF). Thirty adults with type 2 DM were enrolled according to the minimum requirements of the subject required in the preliminary test. All subjects continued to use the same diabetes drug during the study period, and they were asked to attend two visit sessions separated by a week as a washout

period. Each session occurred for 4 consecutive days with two complete 24-hour periods of blood glucose measurement using a continuous glucose monitoring (CGM) system. Participants consumed either carbohydrate mix-fortified LMRN as a low GI meal or CNSF for breakfast at 07:00 AM and snack after dinner at 08:30 PM for two consecutive 24-hour periods (Figure 1). This food is made in Indonesia and has been approved by the National Agency of Drug and Food Control of the Republic of Indonesia with registration number 8625281243.

The food and beverages received by the subjects during the quarantine period were standardized. During the 4-day intervention period with LMRN, the subject received 4,008 kcal with a composition of 519.9 g carbohydrates, 156.74 g protein, 144.78 g fat, and 45.02 g fiber. During the 4-day intervention period with CNSF, the subject received 4,005 kcal with 494.7 g carbohydrate, 147.3 g protein, 159.9 g fat, and 40.12 g fiber. All types of drugs and medication doses were written in the case report form. A sachet of LMRN was dissolved in 200 ml of warm water for each serving, and it became a 250 ml solution after it was dissolved. It was consumed at 07:00 AM and 08:30 PM. Figure 2 presents the flowchart of the study method.

All aspects of the study were explained in the informed consent. Health screening included anthropometric data and a history of food allergies or intolerance, metabolic diseases, and smoking habits. Participants who met all the inclusion criteria, including age 18–60 years, body mass index >18 kg/m², fasting blood glucose ≥ 100 mg/dl, 2 hours after meal blood glucose 140–400 mg/dl, glycated hemoglobin (HbA1c) 7–12%, tolerant to any food, not on medication that could influence the research, and no severe chronic diseases, were enrolled in the study (Table 1).

The study was conducted between January and April 2017 at PT Pharma Metric Labs Indonesia. Ethical clearance was obtained from the Ethical Committee of the Faculty of Medicine Universitas Indonesia

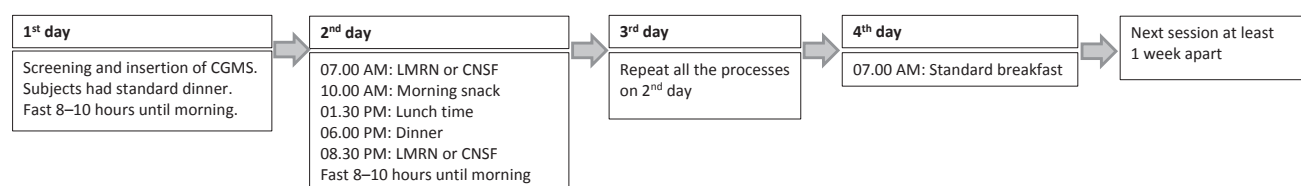


Figure 1. Research flow. CGMS=continuous glucose monitoring system; LMRN=liquid meal replacement nutrition; CNSF=controlled-nutrition solid food

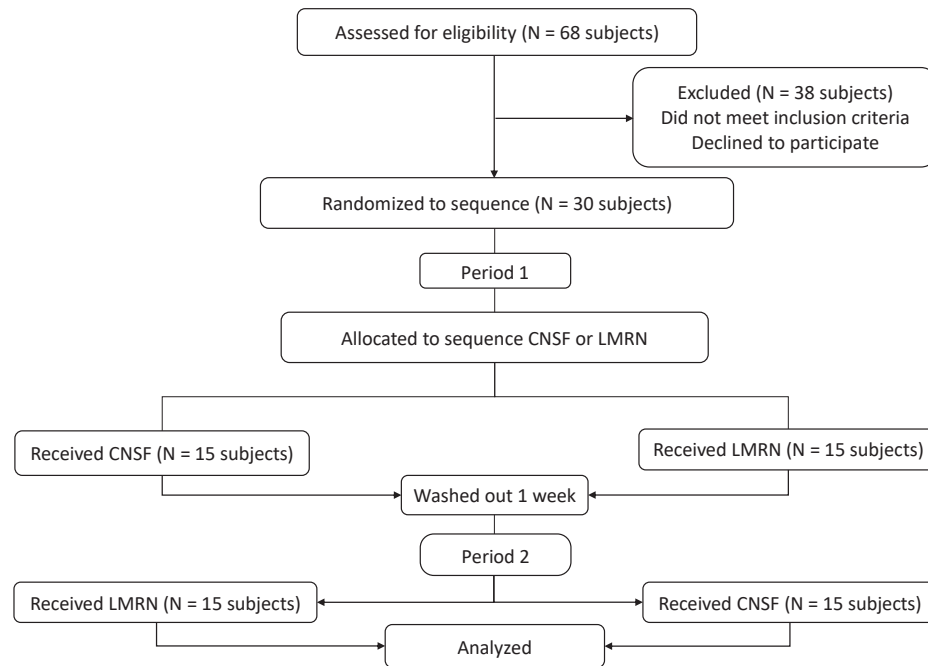


Figure 2. Research flow. CNSF=controlled-nutrition solid food; LMRN=liquid meal replacement nutrition

(No: 809/UN2.F1/ETIK/2016) dated September 19, 2016. Statistical analysis used a power of 85% and a significance level of 0.05.¹⁰

This study used the iPro™ 2 CGM system (Medtronic, USA). The sensor was attached on the first day at 10:00 PM and removed on the fourth day of the study at 07:00 AM. Data analysis was done using the Medtronic software (<https://carelink.minimed.eu>). Glucose reading was recorded every 5 min between 06:00 AM and 06:00 AM for 2 consecutive days (total 48 hours). The sensor was calibrated at each test session—before every meal and before sleeping—using the blood glucose meter (OneTouch® LifeScan, Inc., USA).

Statistical analyses

Statistical analysis was performed after all data were collected and the number of subjects was met. The normality of the data was examined using the Shapiro–Wilk test. The differences in the GR and the iAUC between LMRN and CNSF on days 1 (first 24 hours) and 2 (second 24 hours) were analyzed using paired *t*-test or Wilcoxon test.¹¹ Hypoglycemia incidence, satiety index, number and types of adverse events, and medication used were presented descriptively.

The primary endpoint was to evaluate GR and iAUC. GR is the response of blood sugar following

a meal containing carbohydrates.⁷ The primary outcome of this study was to determine the effects of LMRN and CNSF on the incremental change in glucose (i.e., the GR) over two consecutive 24 hours and for five distinct periods of the day (breakfast, lunch, snack, dinner, and overnight fasting) from 10:00 PM to 06:00 AM. The GR was calculated using the first hour average of CGM interstitial glucose readings under the fasting state as the baseline value. The average baseline glucose value was then used to convert every 5 min reading of 23 subsequent hours of CGMS interstitial glucose data. On the fourth day of the study, the sensor was calibrated 15 min before removal at 10:00 AM. The GR data from the CGMS were converted to “change in glucose” concentration (i.e., the incremental change in glucose) for every 5 min reading for the 23 subsequent hours of CGM data. The other primary outcome measure was the total glucose response expressed as the iAUC.¹²

The secondary endpoint of this study was to evaluate subjective appetite sensations with visual analog scale (VAS), which was given when the subject was consuming LMRN and CNSF in the morning within 2 hours with measurement intervals of 0, 15, 30, 60, and 120 min(s). The VAS is a technique that provides a quantifiable objective

Table 1. Baseline demographic and clinical characteristics of subjects

Characteristic	LMRN to CNSF, mean (SD) (N = 15)	CNSF to LMRN, mean (SD) (N = 15)	Total, mean (SD) (N = 30)
Age (years)	50.91 (13.2)	51.13 (8.4)	50.57 (8.6)
Male sex, n (%)	2 (13)	2 (13)	4 (13)
BMI (kg/m ²)	26.38 (9.21)	25.81 (1.83)	26.07 (3.15)
HbA1c (%)	9.27 (1.26)	9.56 (1.12)	9.44 (1.32)
Fasting blood glucose (mg/dl)	175.37 (33.26)	169.53 (53.94)	172.57 (53.94)
2-hour postprandial blood glucose (mg/dl)	252.49 (63.22)	257.66 (51.14)	254.57 (73.52)
Drug, n (%)			
Only diet	0 (0)	0 (0)	0 (0)
Metformin	7 (47)	8 (53)	15 (50)
Acarbose	1 (7)	2 (13)	3 (10)
Glibenclamide	1 (7)	0 (0)	1 (3)
Metformin + glibenclamide	3 (20)	3 (20)	6 (20)
Metformin + glimepiride	3 (20)	2 (13)	5 (17)

LMRN=liquid meal replacement nutrition; CNSF=controlled-nutrition solid food; SD=standard deviation; BMI=body mass index; HbA1c=glycated hemoglobin

measure translated from subjective sensations and has now been accepted as the standard tool for assessing subjective appetite sensations. These additional features include revealing information that may not be readily inferred from food intake, improve the interpretation of behavior, and allow the measurement of the motivation to eat without contaminating the main behavioral outcome.¹³ VAS typically takes the form of a 100-mm horizontal line with no marker and with a statement at the beginning and end. The questionnaire consists of three questions for measurement: "How hungry do you feel now?"; "How full do you feel now?"; and "How strong is your desire to eat now?"¹³

Evaluation of blood glucose control was performed based on the percentage of hypoglycemia incidence during the intervention period. The criterion of hypoglycemia used in this study was blood glucose levels <70 mg/dl based on CGM or self-reported hypoglycemic symptoms.¹⁴

Safety parameter was observed based on: (1) the number and types of adverse events, including side effects that occurred starting from the screening period until the intervention ended; and (2) the use of medication when there were adverse events such as anti-diarrhea and anti-emetics for diarrhea and vomiting, respectively, including side effects that occurred during the intervention.

RESULTS

The experimental protocol was completed by 30 study participants. All subjects had complete data for both LMRN and CNSF. Results of 48-hour

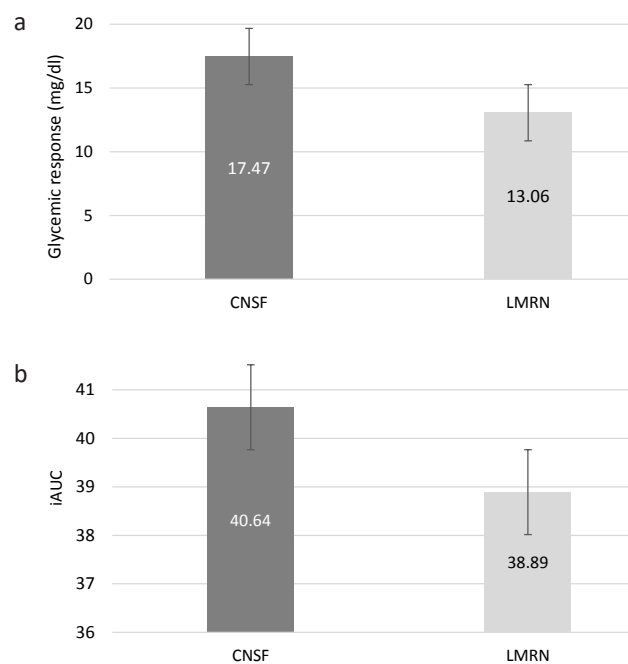


Figure 3. Mean glycemic response for 24 hours (a) and incremental area under the curve (iAUC) (b) for 48 hours in groups consuming controlled-nutrition solid food (CNSF) and liquid meal replacement nutrition (LMRN)

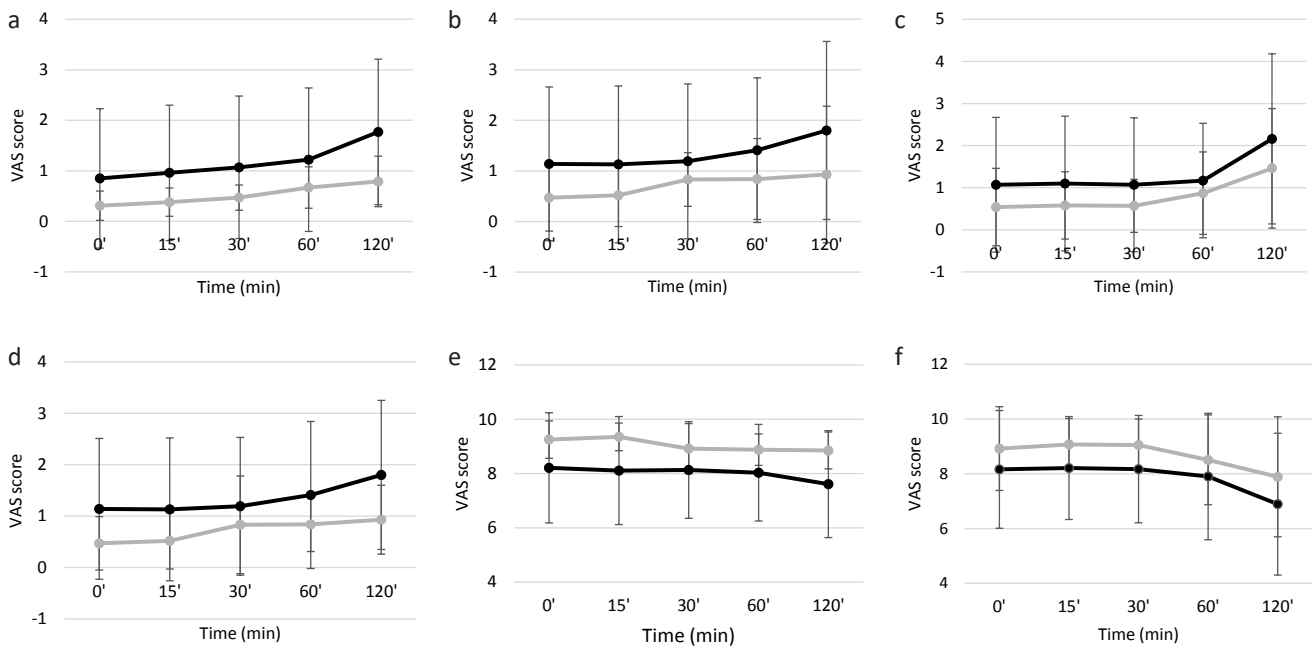


Figure 4. Results of the VAS questionnaire on the first and second 24 hours of: “how hungry the subject felt” (a, b), “how strong is your desire to eat now” (c, d), and “how full the subject felt” (e, f) with measurement intervals at 0, 15, 30, 60, and 120 min(s) in the CNSF (black line) and LMRN (grey line) group. VAS=visual analog scale; CNSF=controlled-nutrition solid food; LMRN=liquid meal replacement nutrition

measurement showed that the mean value of GR was higher in the CNSF group than in the LMRN group ($p>0.5$). The iAUC during 48 hours showed that there was a lower glycemic variability in the LMRN group than in the CNSF group (Figure 3).

Satiety level was measured during the intervention period using the VAS questionnaire when subjects were taking LMRN or CNSF. The VAS questionnaire included statements of “how hungry the subject felt,” “how full the subject felt,” and “how strong the desire of subjects to eat now.”

This present study showed that the VAS at 0, 15, 30, 60, and 120 min(s) for the questions “how hungry the subject felt” and “how strong is the desire of subject to eat now” was lower in subjects consuming LMRN than those taking CNSF. According to the data, when consuming LMRN, the subjects felt less hungry and had less desire to eat (Figure 4).

Table 2. Adverse events

Event	LMRN	CNSF
Vomit	1	0
Soft stool	1	0
Blood glucose 60–69 mg/dl	2	3

LMRN=liquid meal replacement nutrition; CNSF=controlled-nutrition solid food

Results of the research showed that the VAS at 0, 15, 30, 60, and 120 min(s) for the question “how full the subject felt” was higher in subjects consuming LMRN than those having CNSF. Based on the graph, the subjects had a greater satiety level when consuming LMRN (Figure 4).

Based on the CGMS, there were five incidents of blood glucose levels <70 mg/dl, but none reported hypoglycemic symptoms. Other adverse events that may be associated with LMRN were vomiting (one incident) and soft stools (one incident). All the events were mild and did not need any treatment or special procedure to overcome (Table 2).

DISCUSSION

DM is a metabolic disease that is characterized by a hyperglycemia, with biochemical alterations in lipid profile, insulin resistance, and oxidative stress. Dietary intervention can alter the potential consequence of oxidative stress and lipid abnormalities.¹⁵

High GI meals or food causes greater blood glucose levels, induces higher insulin response, and inhibits a glucagon release compared with low GI meals. In patients with type 2 DM, consuming food with a high GI may cause a surge of blood glucose level; therefore, a low glycemic diet is highly recommended

to reduce postprandial hyperglycemia, which may lead to an overall improvement of glycemic control.^{16,17} In this study, the GR profile of blood glucose level was higher in subjects receiving CNSF than those consuming LMRN. It indicates that the GR profile of LMRN can prevent the development of increased gluconeogenesis, which affects carbohydrate metabolism in patients with type 2 DM. Increased postprandial blood glucose level has also been known as one of the causes of cardiovascular disorders in DM patients.¹⁸

The iAUC during the first and second 24 hours (Figure 3) showed that there was a lower glycemic variability in the group consuming LMRN than those taking CNSF. It indicated that there was a higher blood glucose level surge after consuming CNSF. Continuous high glycemic variability may cause activation of oxidative stress. This will induce endothelial dysfunction that may cause vascular damage.¹⁸

The low GI food will cause a lower GR and variability; therefore, the insulin response is not as high as when an individual consumes meal with high GI. It will lead to increased fat oxidation and prolonged satiety. In a clinical trial conducted by Kaur et al,¹⁰ after breakfast consumption of low GI food, there was a significant decrease in calorie intake at lunch. Their study showed that the consumption of low GI food can affect subsequent eating.¹⁰ Consuming meals with low GI during exercise will cause our body to use more fat than carbohydrates for energy; therefore, there is no accumulation of body fat and no weight gain.¹⁹ This study showed that subjects felt less hungry, had less desire to eat, and had a greater satiety level when consuming LMRN (Figure 4).

The most important components contained in LMRN used in this study are isomaltulose, resistant dextrin, and inulin. Isomaltulose or palatinose is a disaccharide composed of fructose and glucose in an α -1,6-glycosidic bond. Isomaltulose has 32 GI of carbohydrate that provides a sustained glucose release and reduces the increase in insulin and blood glucose level after a meal compared with sucrose. The absorption and hydrolysis process of isomaltulose in the mucosa of the small intestine is slower, so the absorption and metabolism of monosaccharides (glucose and fructose) occur more perfectly while producing a lower GR.²⁰ Maresch et al²⁰ reported that the benefit of replacing sucrose

with isomaltulose includes the significant influence of improving glycemic control in the nondiabetic population. Consuming isomaltulose for 12 weeks may improve insulin sensitivity and reduce fat oxidation compared with taking sucrose.²¹ A resistant dextrin is a polysaccharide with α -1,2 or α -1,3 bonds, and it is included in the prebiotics. Resistant dextrin compound generates 7.1 up to 8.4 kJ/g energy (1.7 up to 2.0 kcal/g). Its mechanism of action in the body is to activate the differentiation of L cells in the colon and increase hormones that play a role in regulating appetite and controlling glucose metabolism and insulin resistance, such as peptide YY, gastric inhibitory polypeptide, glucagon-like peptide (GLP), GLP-1, and GLP-2.²¹ Increased GLP-1 levels will result in increased glucose uptake in the muscles, resulting in decreased blood glucose levels and increased nitric oxide levels in the blood, thereby improving endothelial function. Increased GLP-2 levels will normalize the ratio of Gram-negative and Gram-positive bacteria, resulting in lower permeability of the gastrointestinal tract and decreased levels of endotoxin. Decreased endotoxin is beneficial for the body because it reduces the inflammatory process and insulin resistance. GLP-2 hormone also influences the activation of the phosphatidylinositol 3-kinase signal, so it can improve glucose homeostasis and insulin sensitivity.²²

The supplementation of resistant dextrin will increase the production of butyrate and propionate. This mechanism may lead to activating receptors of G-protein and free fatty acid, resulting in increased secretion of peptide YY, GLP-1, and gastric inhibitory polypeptides. Butyrate, which is a short-chain fatty acid (SCFA), can activate the expression of peroxisome proliferator-activated receptor gamma, which increases fatty acid oxidation in the muscle, leading to reduced insulin resistance. The resistant dextrin, as prebiotic, can increase GLP-2 hormone and reduce endotoxin levels and inflammation.²³

Inulin is a natural polymer with fructose monomers containing about 35 units of fructose, which are bound by a straight chain with a β -21 glycoside bond. It is a food component produced by various plants, and it is stored in the roots or bulbs, such as the bulbs of dahlia, chicory, onion, garlic, banana, and wheat. Inulin is indigestible by ptyalin and amylase enzymes, but it can be fermented by microflora in the colon; therefore, it is categorized as prebiotics. It can also selectively

stimulate the growth and activity of gut microbiota, which can improve and protect the intestine and reduce the risk of gastrointestinal disorders such as colon cancer. Inulin fermentation product is produced by *Bifidobacteria* and *Lactobacilli*, including SCFA and L-lactate. Major products of SCFA are acetate, propionate, and butyrate.²⁴ In carbohydrate metabolism, propionate is converted into methylmalonyl-CoA that inhibits pyruvate carboxylase enzyme, which is a catalyst of phosphoenolpyruvate (PEP) from pyruvate. PEP is a precursor for glucose production in the gluconeogenesis pathway. Inulin supplementation may inhibit the formation of PEP so that gluconeogenesis will not occur and blood glucose levels may be reduced. Another advantage of inulin is that it has lower calories than other types of carbohydrates, so it does not affect the blood glucose level, stimulate insulin secretion, and affect glucagon secretion. Another advantage of substituting sugar with inulin is that inulin has only one-third to one-fourth calorie of sugar and one-ninth calorie of fat. It also facilitates calcium and magnesium absorption in the intestines.²⁴

This study provides evidence that there is a lower blood glucose level in subjects consuming LMRN than in those taking CNSF and that the subjects felt less hungry. It indicates that isomaltulose, resistant dextrin, and inulin are beneficial in lowering blood glucose levels and prolonging satiety. Further studies are recommended using LMRN products with different compositions for comparison and with longer interventional time, for example, 3 months, to evaluate the HbA_{1c}.

In conclusion, this study shows there are lower GR and iAUC on the 48 hours following LMRN compared with CNSF. The daily blood glucose level was more stable following the use of LMRN than CNSF. A comparison of VAS at an interval of 0, 15, 30, 60, and 120 min(s) showed that the LMRN group felt less hungry and had a greater satiety level than the CNSF group. Carbohydrate mix-fortified LMRN provides longer term satiety than CNSF. Administration of LMRN does not have any serious adverse effects.

Conflict of Interest

Fatimah Eliana received non-financial support from PT Sanghiang Perkasa. Budi Agus Pranoto was an employee of PT Sanghiang Perkasa, during the conduct of the study.

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