

# Efficacy of a Novel Low-Glycemic-Index Medical Food on Satiety and Gut Hormone Responses in the Normal-Weight and Obese

Rattikan Sumpao<sup>1</sup>, Preeya Leelahagul<sup>1</sup>, Siriporn Tuntipopipat<sup>2</sup>, Thanwarin Tangsermwong<sup>3</sup>, Chawanphat Chawanphat<sup>2</sup>, Wutarak Puengputtho<sup>1</sup>, Kemika Praengam<sup>2</sup>, Surat Komindr<sup>4,\*</sup>

<sup>1</sup>Department of Nutrition, Ramathibodi Hospital and Institute of Nutrition, Mahidol University, Bangkok, Thailand <sup>2</sup>Cell and Animal Model Unit, Institute of Nutrition, Mahidol University, Nakhon Pathom, Thailand <sup>3</sup>Division of Nutrition and Dietetics, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand <sup>4</sup>Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand \*Corresponding author: surat.kom@mahidol.ac.th

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**Abstract** Low glycemic index medical food (LGI) has been utilized as a meal replacement for patients with type 2 diabetes, obesity, and improving other metabolic outcomes. However, since the impact of this diet on hormones and satiety is unclear, this study determined the effect of a novel LGI on satiety and gut hormone responses in normal-weight and obese adults. Methods: The study was a randomized, cross-over, single-blind controlled trial. Healthy adults aged 20-45 years consisting of 20 normal weight (NW) and 20 obese (OB) as classified by % body fat. Each subject was assigned to drink the soybean milk (SB) as a control and the novel LGI breakfast (ONCE PRO<sup>®</sup>) as a test meal in a random order, with a seven-day washout period. Their satiety was assessed with a visual analog scale (VAS) questionnaire before and every 30 minutes after each breakfast for 240 minutes. Plasma GLP-1, ghrelin, and total PYY were measured at baseline, 30, 60, 120, and 240 minutes after breakfast. After 240 minutes, subjects were given a buffet lunch to eat until satiated and total lunch intake was recorded. Results: Both NW and OB had significantly higher GLP-1 and PYY AUCs and significantly lower ghrelin AUCs (both NW and OB; GLP-1 p<0.0001, PYY p<0.01, and ghrelin p<0.001) after the novel LGI compared to SB, which were related to the satiety and hunger scores. After the novel LGI, both groups rated themselves as less hungry and fuller than SB. Moreover, ghrelin AUC of OB was significantly lower than NW (p < 0.05) after consuming the novel LGI which was related to a significantly lower hunger score (p < 0.05) and a tendency to eat less lunch than after SB. Conclusions: The novel low glycemic index medical food had superior effects on gut hormones and satiety improvement over soybean milk in both NW and OB subjects. Furthermore, OB tended to be more influenced by the novel LGI than NW on the hormonal changes and decreased eating.

Keywords: low glycemic index, meal replacement, satiety, glucagon-like peptide 1, ghrelin, peptide YY

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# **1. Introduction**

Satiation is the sensation that happens when an individual consumes a certain quantity of food or beverage. When the person feels full, they want to stop eating or drinking. Satiation is influenced by a variety of variables, including the environment, social circumstances, and genetics. High satiety effect refers to the sensation of being full after a previous meal. Previous research established that nutrients in diets were the important factors to regulating satiety, energy intake, and body weight [1]. Consuming foods that provide a high level of satiety is one strategy for weight control.

Satiety sensation, as a result of gastrointestinal hormones that influence appetite regulation. The hormone increasing appetite is ghrelin, whereas active glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) are inhibiting [2,3]. Type of food consumption affects those hormones' level change and consequence to appetite level [4]. A high-protein diet with carbohydrates increases GLP-1 production. Currently, we know that GLP-1 treatment decreases food intake, appetite, and hunger while increasing fullness and satiety, resulting in weight reduction [5]. Furthermore, only high protein diet-induced satiety is mainly associated with higher energy expenditure which increases oxygen consumption and body temperature, which contributes to feeling of oxygen derivation and thus promotes satiety [6]. The effect of a carbohydrate on satiety depends on the form of the carbohydrate and other aspects of the food such as fiber content [7]. High glycemic index foods will enhance hunger and calorie intake because they raise blood glucose and increase appetite. Conversely, meals with a low glycemic index will increase satiety which helps obese or diabetic patients manage their weights and blood glucose levels [8].

The novel low glycemic index medical food (LGI) has been used as a meal replacement for patients with type 2 diabetes (T2DM), to reduce hyperglycemia, hyperlipidemia, and body weight [9]. However, since the impact of this diet on hormones and satiety is unclear. We were interested in examining the influence of the novel LGI and soybean milk as breakfast on satiety and gut hormonal changes, i.e. ghrelin, GLP-1, and PYY and intake of subsequent meals in normal-weight and obese persons.

## 2. Subjects and Methods

This study was a single-blind, randomized, cross-over, controlled trial. The study was approved by the ethical standards for clinical research by the Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University, research ID 04-61-14.

Table 1. Nutritional composition of soybean milk (SB) and the novel low glycemic index medical food (LGI) administered in the study, 1 serving = 300 ml

Main ingredients	SB	novel LGI
Total Protein (g)	16.0	16.0
Whey protein isolate	_	8.0.50.0%
(g, % total protein)		0.0, 50.070
Soy protein isolate	16.0, 100%	8.0, 50.0%
Total Carbohydrate (g)	34.2	38.8
Sucrose (g, % total carbohydrate)	21.2, 62.0%	-
Maltodextrin	10.0, 29.2%	18.3, 47.2%
Isomaltulose	-	7.1, 18.3%
Maltitol	-	7.1, 18.3%
Fibersol-2	-	3.5, 9.1%
Fructooligosaccharides (FOS)	-	1.8, 4.6%
Dietary fiber	3.0, 8.8 %	-
Others (e.g. flavors)	-	1.0, 2.5%
Total Fat (g)	14.5	14.5
Canola oil (g, % total fat)	-	7.10. 48.8%
High oleic safflower oil	-	3.5, 24.40%
Rice bran oil	-	3.2, 21.99%
Fish oil	-	0.7, 4.81%
Soybean oil	14.5,100%	-
Total calorie (kcal)	327.33	327.33
Caloric distribution		
(Protein: Fat: Carbohydrate)	20:40:40	20:40:40

The research enrolled healthy people aged 20 to 45 years with BMI between 18.5 to 34 kg/m2 consisting of those who were normal weight (NW) (n=20) and obese (OB) (n=20) based on their body fat percentage (% BF). The obesity was determined according to % BF in each age-group and sex; % BF  $\geq$  33 % of BW in females aged 20-39 years or  $\geq$  34 % of body weight (BW) if aged 40-45 years and  $\geq$  20% of BW in males aged 20-39 years, 40-45 years. Participants taking weight loss medications or supplements that may have affected appetite, as well as participants with liver, kidney, thyroid, anemia, and infectious diseases detected during screening blood

examinations were excluded from the study. The body composition parameters and basal metabolic rate were determined using Tanita BC-420 Body Composition Analyzer (Tanita Co.Ltd., Japan). The purpose and procedures for the study had been informed, and the consent forms were signed by all subjects. Subjects were instructed by dietitians on how to properly record 24-hour dietary records. All were assigned to drink both soybean milk (SB) and the novel low glycemic index medical food (LGI) GI = 27.29, (ONCE PRO<sup>®</sup> Thai Otsuka Pharmaceutical Co., Ltd.) in a random order, both nutritional compositions are shown in Table 1.

Subjects attended the clinical research center on two occasions, separated by a one-week washout period during which subjects were asked to maintain their regular diet and to complete the 24-hour dietary records. On the test day, after a 12-hour overnight fast, subjects were given 300 ml of either SB or the novel LGI both at 8 a.m., both providing 327.33 kcal, and were allowed to sip water up to 300 ml till noon. Lunch was offered ad libitum four hours after breakfast, and participants kept track of their total lunch intake. The participants were closely observed by a dietitian throughout the trial.

#### 2.1. Satiety and Food Intake Assessments

The visual analog scale (VAS) was used alongside measures of food intake. The appetite questionnaires were created to evaluate satiety (fullness and hunger). Subjects were instructed to mark a point on the scale within the anchored points that reflected their feelings regarding each question. The VAS test was repeated every 30 minutes, 9 times, between 8.30 to 12 a.m. For 24 hr food intake records, subjects were taught to record food intakes by dietitians for collecting dietary intake data each day before 7 days of enrolment visit and study visit.

#### **2.2. Blood Sampling**

Before the start of the study, blood was collected from subjects after a 12-hour overnight fast for screening of hemoglobin, fasting blood sugar, BUN, creatinine, uric acid, total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, SGOT, and SGPT using an automated blood BS-400 Chemistry Analyzer (Mindray Bio-Medical Electronics Co. Ltd, China). During the test day, venous blood samples were obtained from individuals at 7-8 a.m. following a 12-hour overnight fast (t = 0), then at 30, 60, 120, and 240 minutes (t = 30, 60, 120, and 240) after breakfast for measurement of ghrelin, active GLP-1, and total PYY using Milliplex<sup>®</sup> MAP kits (Merck Millipore, Germany).

#### 2.3. Statistical Analyses

Data are expressed as mean and standard deviation (SD) in the tables and standard error of the mean (SEM) in the figures. Repeated measure ANOVA was used to determine differences between body composition, energy intake, and biochemistry data within group. The area under the curve (AUC) for each hormone was calculated from the plotted data using the Trapezoid Method. In addition, an independent t-test was used to compare the difference in body composition, energy intake, and biochemistry data between groups. Pearson's correlation 95% confidence interval was used for correlation analysis between body composition and biochemistry data. Results were considered significant if p < 0.05 SPSS statistics 23.0 for Windows was used for statistical analysis.

# 3. Results

#### 3.1. Subjects Characteristics

Forty healthy adults consisted of 20 normal weight (NW) and 20 obese (OB). The two groups had a similar gender distribution. Bodyweight, BMI, body fat percentage, and hemoglobin levels differed between the NW and OB groups, but other values were not different. The baseline demographic and biochemical characteristics of subjects are shown in Table 2.

#### **3.2. Satiety Assessment**

The visual analog scale questionnaires were completed before and every 30 minutes after breakfast between 8.30 am and 12.00 am to measure satiety score as shown in Figure 1.

There was no significant difference in fullness score (Panel A) in NW and OB subjects at 0 minute. Although the fullness score of all subjects had continued to decline

at 120, 150, 180, 210, and 240 minutes, there was no difference in the fullness score after both diets. There was no significant difference in the hunger score (Panel B) between NW and OB subjects at 0 minute. However, the hunger score of the novel LGI breakfast was significantly lower than SB breakfast at 90 minutes and continued to be less than SB breakfast until 240 minutes in the NW group. While in OB group, hunger score after the novel LGI breakfast were lower than SB breakfast significantly at 30, 120, and 240 minutes. There were no significant differences in the desire for something sweet, salty, savory, and fatty.

Table 2. Subjects Characteristics (n= 40)

Parameter	NW (n=20)	OB (n=20)	
Male/Female (n)	10/10	10/10	
Age (years)	$32.95 \pm 6.44$	$33.00\pm6.36$	
Weight (kg)	$59.99 \pm 9.27$	$80.67 \pm 14.36^{*}$	
Height (cm)	$163.60\pm6.20$	$165.55\pm4.30$	
BMI (kg/m2)	$22.06 \pm 1.79$	$29.68 \pm 4.01^{*}$	
Total body fat (%BW)	$22.53 \pm 6.00$	$34.37 \pm 7.08^{*}$	
Hemoglobin (g/dL)	$13.76 \pm 1.61$	$14.35 \pm 1.56^{*}$	
FBS (mg/dL)	$85.40 \pm 6.92$	$88.60 \pm 6.85$	
BUN (mg/dL)	$13.10\pm3.03$	$12.73\pm3.08$	
Cr (mg/dL)	$0.91\pm0.19$	$0.96\pm0.18$	
SGOT (U/L)	$20.30\pm4.93$	$21.50\pm5.80$	
SGPT (U/L)	$16.00\pm9.39$	$24.90 \pm 8.97$	

The Normal-weight (NW) and Obese (OB) Groups. Values are reported as mean values  $\pm$  standard error of the mean; significant difference from NW group: \* p < 0.001.





"How hungry do you feel?"



Figure 1. Satiety assessment on fullness (A) and hunger (B) of all subjects with Visual Analog Scale (VAS) after consumption of soybean milk (SB) and the novel low glycemic index medical food (LGI) breakfast. Values are reported as mean values  $\pm$  standard error of the mean. Significant difference from SB; \* p < 0.05

#### 3.2. Dietary Intake

INMUCAL Nutrients version 3.0, a nutritional calculating program for Thai foods created by the Nutrition Institute of Mahidol University of Thailand, was used to compute all of the subjects' energy and nutrient intakes. The daily energy intakes of SB and the novel LGI over the seven days before testing were not substantially different. Daily, the NW group consumed much less energy than the OB group. There were no statistically significant differences in the average energy consumption for breakfast and lunch within or between the NW and OB groups, due to the fact that each person's diet is individual. The mean energy intake of ad libitum lunches after the test breakfast is shown in Table 3.

Energy consumed at lunch after the novel LGI meal was less than the amount obtained after SB. However, it was not statistically significant. The NW subjects who ate the novel LGI meal lowered their calorie consumption at lunch by 3% when compared to SB. Obese subjects, furthermore, were able to cut their energy consumption down by more than 7%. Seven subjects reduced their lunch by more than 200 kcal when compared to SB breakfast, whereas four subjects increased their consumption after the novel LGI.

#### 3.3. Gut hormones

Blood was collected before breakfast, 30, 60, 120, and 240 minutes after breakfast for gut hormone analysis. The results of NW and OB groups are shown in Figure 2.

Table 3. The Dietary Intake for Lunch after Soybean milk (SB) and the Novel Low Glycemic Medical Food (LGI) Breakfasts of Normal-weight (NW) and Obese (OB) Groups

	NW (n=20)		<b>OB</b> (n=20)	
	SB	novel LGI	SB	novel LGI
Total Energy (kcal)	$582 \pm \! 60.6$	$553\pm39.7$	$679 \pm 62.9$	$626\pm 38.2$
Carbohydrate (g)	$69.6\pm9.9$	$62.0\pm 6.8$	$72.2\pm7.7$	$63.8\pm4.6$
Protein (g)	$31.5\pm2.4$	$31.7\pm1.7$	$37.9\pm2.9$	$36.3\pm2.4$
Fat (g)	$19.7\pm2.0$	$19.8 \pm 1.5$	$26.4\pm2.7$	$25.1\pm1.7$

Values are reported as mean values  $\pm$  standard error of the mean. There were no significant differences between groups.



**Figure 2.** Plasma levels and area under the curve (AUC) of GLP-1(A, B) PYY(C, D) and ghrelin (E, F) in normal weight (NW), n=20, and obese (OB) groups, n=20 after soybean (SB) and the novel low glycemic index medical food (LGI) breakfast, Values are reported as mean values  $\pm$  standard error of the mean. Significantly different from SB at the same time point; \* p < 0.05, \*\* p < 0.01, +p < 0.005, ++ p < 0.001, +++ p < 0.001



**Figure 3.** The area under the curve (AUC) of GLP-1, PYY, and ghrelin in normal weight (NW); n=20 and obese (OB); n=20 groups after soybean (SB) and the novel low glycemic index medical food (LGI) breakfast. Percent change in hormones is shown by up-down arrows. Values are reported as mean values  $\pm$  standard error of the mean. Significantly different from SB; \*\* p < 0.01, ++ p < 0.001, +++ p < 0.0001. Significant difference from NW group;  $\alpha$  p < 0.05

In the NW group, all hormone levels were not significantly different at baseline (0 minute). Then the levels of GLP-1, and PYY rise rapidly until it reaches a maximum at 60 minutes. Interestingly, within 30 and 60 minutes after consuming the novel LGI, both GLP-1 and PYY had significantly higher levels than consuming SB (GLP-1; 30minutes: p < 0.01, 60 minutes: p < 0.0001 and PYY; 30 minutes: p < 0.005, 60 minutes: p < 0.0001 and continued higher level after 120 minutes (Figure 2). This also correlates with the areas under the curve (AUC) that GLP-1 and PYY after the novel LGI breakfast were significantly greater than SB (GLP-1: p < 0.0001, PYY: p < 0.01) as seen in Figure 3. Ghrelin levels dropped slightly in all types of breakfast until 30 minutes, and significantly dropped after 60 minutes in the novel

LGI (p < 0.05). They continued dropping until 240 minutes while on SB was rising (p < 0.0001). This resulted in ghrelin AUC after the novel LGI breakfast was significantly lower than after SB breakfast (p < 0.001).

In the OB group, the graph characteristics were similar to those in the NW group. After consuming the novel LGI, GLP-1 and PYY levels are higher than consuming SB after 30 minutes. GLP-1 levels after the novel LGI breakfast were significantly higher than SB at 30 to 60 minutes (30 minutes: p < 0.005, 60 minutes: p < 0.05). While the PYY levels after having the novel LGI breakfast were significantly higher than SB at all points of time from 30 to 240 minutes (p < 0.05). The AUC of GLP-1 and PYY of after the novel LGI breakfast were significantly novel LGI breakfast were significantly higher than SB at all points of time from 30 to 240 minutes (p < 0.05). The AUC of GLP-1 and PYY of after the novel LGI breakfast were significantly greater than SB (GLP-1: p < 0.0001, PYY:

p < 0.01). A part of same as NW group, ghrelin levels fell slightly in all kinds of breakfast until 60 minutes, then the novel LGI continued to drop while SB was increasing and significantly differed at 120 to 240 minutes (120 and 240 minutes: p < 0.0001). As a result, the AUC for ghrelin after the novel LGI breakfast was significantly lower than after SB breakfast (p < 0.001). Remarkably, all hormones AUC after the novel LGI differed significantly from those after SB intake, as seen in Figure 3. The percentage change in hormones among NW patients was reported in decreasing order as GLP-1 85.45%, PYY 46.15%, and ghrelin 43.25%. In contrast, the GLP-1 in OB subjects had the greatest percentage change, increasing to 128.4 % of SB AUC followed by ghrelin and PYY at -45.9 % and 21.8%, respectively. Ghrelin AUC of OB subjects was significantly lower than NW subjects (p < 0.05).

Overall, the subjects who had the novel LGI for breakfast had significantly higher levels of GLP-1 and PYY and a lower level of ghrelin than the subjects who had SB in both NW and OB groups.

## 4. Discussion

Soybean milk (SB) is commonly being consumed in Asian cultures, as part of the morning meal. It was chosen as the control meal for this experiment. Both SB and the novel LGI breakfasts in the trial were modified to make both meals as similar as possible in terms of energy and main composition. Hence, the various gut-hormone (GLP-1, PYY, and ghrelin) responses to satiety control [2,3] are mostly due to the presence of different ingredients. After consuming the novel LGI, the quantity of GLP-1 and PYY increased up to 120 and 40%, respectively compared to SB. Protein usually promotes satiety and reduces hunger more than carbohydrates or fat and may help reduce energy intake under the circumstances of ad libitum diet [10,11,12]. However, both diets contained about the same amount of protein, which accounted for 20% of total calories. Unlike SB which includes entirely soy protein, the novel LGI contains whey protein as much as 50% of protein content. Numerous studies indicated that whey protein promotes satiety, and GLP-1, which is currently being used for weight control [4]. Whey protein and maltodextrin may help with satiety and decreased hunger more than soy protein [13] by raising GLP-1, PYY and reducing ghrelin levels over 3 hours, the effects are dosedependent [14]. In comparison with previous studies, preload whey protein increased plasma GLP-1, CCK and GIP and reduced energy of buffet meal ad libitum intake by 10% compared to eating the same amount of casein for the same amount of time [15]. The specific amino acids in whey protein were associated with the appetite-suppressant and GLP-1-stimulating by their binding with nutrient-sensing receptors expressed by L cells within the gastrointestinal wall [16]. The impact of these hormonal changes was also consistent with prolonged fullness and delayed hunger, in the present study in which participants reported feeling less hungry after consuming the novel LGI diet. Additionally, it has a sequential impact on lunch consumption. After consuming the novel LGI, subjects were more inclined to eat less than after consuming SB. Meanwhile, ghrelin, the hunger hormone, has fallen 40% after consuming the novel LGI breakfast compared to SB and is still lower after 240 minutes passed. Other factors that affect the hormone GLP-1 stimulation, including the slow-release carbohydrates and high fiber content. Isomaltulose rather than the same amount of sucrose [17], and maltitol in low glycemic index food has been reported to increase GLP-1 AUC [18]. The novel LGI breakfast contains 3.55 g of Fibersol-2, a soluble dietary fiber can also increase plasma GLP-1 and PYY levels and slow hunger as shown by Zhong Ye et al [19]. From the above mentioned, the novel LGI contains more satiating components than SB. In addition, the mean ad libitum lunch intake of NW group after the novel LGI breakfast was about 3% less than after SB breakfast, whereas the lunch intake of OB group after the novel LGI breakfast about 7% less. This is similar to previous research by Emilia et al. [20] that low glycemic index snacks had a greater effect on satiety by reducing lunch energy intake 6.3%, and Jimenez-Cruz et al. [21] found that meals with low glycemic index, high protein, and fiber content help to keep the stomach full longer and lower lunch intake. Moreover, the present study revealed that after consumption of the novel LGI breakfast, OB had delayed regaining of hunger and significant suppression of ghrelin level more prominent than NW. Thus, intake of the novel LGI medical food affects short-term satiety perception. However, long-term studies on the novel LGI have also been published. Umphonsathien et al. [22] previously conducted a 20-week intermittent substitution of the novel LGI for regular breakfast could help T2DM patients reduce weight and BMI significantly. Another large and long-term European study also demonstrated that subjects following the low glycemic index and high protein diet could reduce weight, fat mass, and waist circumference more than the control group after a 26week trial [23].

# 5. Conclusion

Our study has demonstrated the combined impact of variety satiety-stimulating substances in a specific diet that may be utilized in everyday life. This research concluded that the novel LGI contributed to greater satiety and less hunger than SB breakfast as supported by the evidence that the novel LGI significantly improved the gut hormone levels (GLP-1, PYY and ghrelin). Individuals taking the novel LGI breakfast were more inclined to decrease their lunch consumption. This hormonal impact is the result of the formula's various components contained in the novel LGI. No adverse effect has been reported. The OB experienced greater changes than NW in GLP-1 and ghrelin levels and delayed hunger, with a tendency to lower lunch intake. It is anticipated that the novel LGI medical food would be a useful tool for healthy weight management.

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