**(別紙様式第 2 号)**

令和元年度 学位論文

**(論文題目)**

# Substituting Pre-Germinated Brown Rice for White Rice Reduced Body Weight in Healthy Overweight Vietnamese Women

発芽玄米が健康な過体重のベトナム女性の体重におよぼす影響

十文字学園女子大学大学院
人間生活学研究科
食物栄養学専攻

**(学位申請者氏名)**

**Vu Anh Linh (学籍番号 17DA001)**

審査委員

主：池川 繁樹（教授）

副：岩本 珠美（教授）

副：山本　茂（教授）

指導教員 **(氏名) (職位)**

主：　山本　茂　（教授）

副：　長尾　昭彦（教授）

副：　岩本 珠美　（教授）

**Contents**

## ABSTRACT

***Background:*** We have reported that newly diagnosed type 2 diabetes mellitus (DM) occurs in Vietnamese who have a low body mass index (BMI) of around 23, which is normal for Japanese. We also found that the major factor for this condition is high white rice (WR) intake. Brown rice (BR) is known to be beneficial in the control of blood glucose levels; however, it is difficult to eat. Pre-germinated brown rice (PGBR) is slightly germinated by soaking BR in water as this reduces the hardness of BR and makes it easier to eat. Some short-term studies in Vietnam, Japan, and Taiwan suggest that PGBR may help to reduce the risk of high blood glucose and lipid concentrations. There are studies that have shown the effectiveness of PGBR on high blood glucose and cholesterol concentrations mainly in DM patients but only a few studies have investigated the effect on body weight, perhaps because the subjects are usually instructed to reduce their energy intake and the change in body weight from foods is difficult to observe.

Therefore, in our previous study, on impaired glucose tolerance (IGT) not DM, we studied effect of a 4-mo PGBR administration on concentrations of blood glucose and lipids as well as on body weight. The subjects were Vietnamese women aged 45-65 years old living near Hanoi City. Thirty matched pairs were established by screening through fasting glucose measurement and then by a glucose tolerance test. During the intervention period, subjects were instructed to consume either WR or PGBR as a staple food over 4 mo. The results suggest that replacing WR with PGBR for 4 mo may be useful in controlling body weight as well as blood glucose and lipid levels in Vietnamese women with IGT. With such a background, in this study we tried to observe the effect on body weight in healthy over-weight women.

***Purpose:*** To study the effect of PGBR on weight reduction in healthy overweight Vietnamese women.

***Design:*** The study was a randomized control trial that was conducted in 72 healthy overweight women. All participants were randomly assigned to consume PGBR or WR as staple foods for 16-weeks. Anthropometric parameters, blood pressure, physical activity, and a nutrition survey were conducted at baseline, 8-week, and 16-week. Fasting blood was withdrawn and biochemical analysis was conducted at baseline and 16-week. Acceptability was ascertained by questionnaire after the study. *Results:* After the 16-week intervention, body weight in the PGBR group decreased from 63.3 ± 6.5 kg to 61.2 ± 6.5 kg ($p < 0.001$), while body weight in the WR group was maintained. Waist and hip circumferences in the PGBR group decreased, for waist -3.6 cm;( $p < 0.001$) and hip -1.8 cm; ($p < 0.001$) but not in the WR group except waist -1.7 cm (p<0.05). Serum total cholesterol and triacylglycerol concentrations (mg/dL) were abnormally high in both groups at baselines; however, at 16-week the PGBR group decreased from 205 to 182 ($p < 0.001$) and from 133 to 108 ($p < 0.05$), respectively, but not the WR group. Energy intakes (kcal/day) in the PGBR group decreased significantly ($p < 0.05$) at baseline, 8-week, and 16-week they were 1912, 1857 and 1803, respectively but not in the WR group (1902, 1882 and 1879, respectively).

***Conclusion:*** These findings suggest positive effects of PGBR on controlling body weight in overweight healthy women as well as on the blood lipid and glucose profiles.

# 発芽玄米が健康な過体重のベトナム女性の体重におよぼす影響


要旨

**背景：**ベトナム人で新たに 2 型糖尿病（DM）と診断された者の Body Mass Indes（BMI）は約 23 で、これは日本人の正常値である。この主な要因は、白米の摂取量が多いことと考えられる。玄米は血糖値の調節に有益であることが知られている。しかし、硬く食べにくい。発芽玄米は、玄米を水に浸し、わずかに発芽させたものであるために柔らかく食べやすい。ベトナム、日本、台湾でのいくつかの短期研究では、発芽玄米が高血糖と脂質濃度のリスクを減らすのに役立つことが報告されている。主に 2 型糖尿病（DM）患者の高血糖およびコレステロール濃度に対する発芽玄米の有効性を示した研究があるが、糖尿病の被験者は通常エネルギー摂取量を減らすように指示されているために、食品によって体重が低下するかどうかはわからない。したがって、我々は以前の研究で、DM のハイリスク者(DM ではない)を被験者にして、4 か月間の PGBR 投与が血糖値と脂質濃度、および体重に及ぼす影響について調査した。対象者は、ハノイ市に住む 45～65 歳のベトナム人女性であった。空腹時グルコース測定によるスクリーニングと、その後の耐糖能試験の結果から 30 組のペアを作り、ランダムに２群に分けた。被験者には白米または発芽玄米を主食として 4 カ月間摂取してもらった。その結果、発芽玄米は、ＤＭのハイリスクのベトナム人女性の体重と血糖値および脂質レベルの改善に有効であることが観察された。このような背景から、本研究では健康な人でも同様の効果が期待できるかどうかを見るために、過体重であるが健康な女性の体重の影響を観察せんとした。

**目的：**健康な太りすぎのベトナム人女性の体重減少に対する発芽玄米の効果を明らかにする。

**方法：** 72 人の健康な太りすぎの女性を対象にランダム化比較試験を実施した。すべての参加者は、16 週間の主食として発芽玄米あるいは白米を主食として食べてもらった。体位、血圧、身体活動、および栄養調査は、ベースライン、第 8 週、および第 16 週で実施した。空腹時の血液をベースラインおよび 16 週間目に採取して生化学分析を行った。また、試験後に嗜好に関するアンケート調査を行った。

**結果：**16 週間の介入で発芽玄米群の体重は 63.3±6.5 kg から 61.2±6.5 kg に減少した（$p < 0.001$）が、白米群では変化しなかった。 発芽玄米群のウエスト周とヒップ周は減少した（ウエスト-3.6±2.0 cm、$p < 0.001$）およびヒップ-1.8±2.2 cm、$p < 0.001$））が、白米群では変化がなかった。ベースラインおよび 16 週目の血清総コレステロールおよび LDL コレステロール濃度（mg / dL）は、それぞれ 205 から 182（$p < 0.001$）および 133 から 108（$p < 0.05$）に低下したが、白米群では変化がなかった。発芽玄米群のエネルギー摂取量（kcal /日）は、ベースライン、8 週間目、および 16 週間目で 1912 から 1857、および 1803 に有意に減少したが、白米群では、1902、1882 および 1879 で変化が見られなかった。試験後の嗜好に関するアンケートで、ほとんどの人が、発芽玄米は白米と同くらいおいしかったと答えた。

**結論：**発芽玄米は、健康であるが過体重のベトナム女性の体重改善に有効であるあることが示唆された。

# I. INTRODUCTION

Rice is one of the main cereals produced world–wide and the major staple food for almost half of the world population that currently eat rice as a staple food. Rice harvested as paddy rice, which consists of the hull, including the lemmae, the larger lemmae, and the caryoposis. The rice caryopsis or called brown rice (BR) is comprised of the pericarp, seed coat, nucellus, aleurone layer, endosperm, and the embryo.

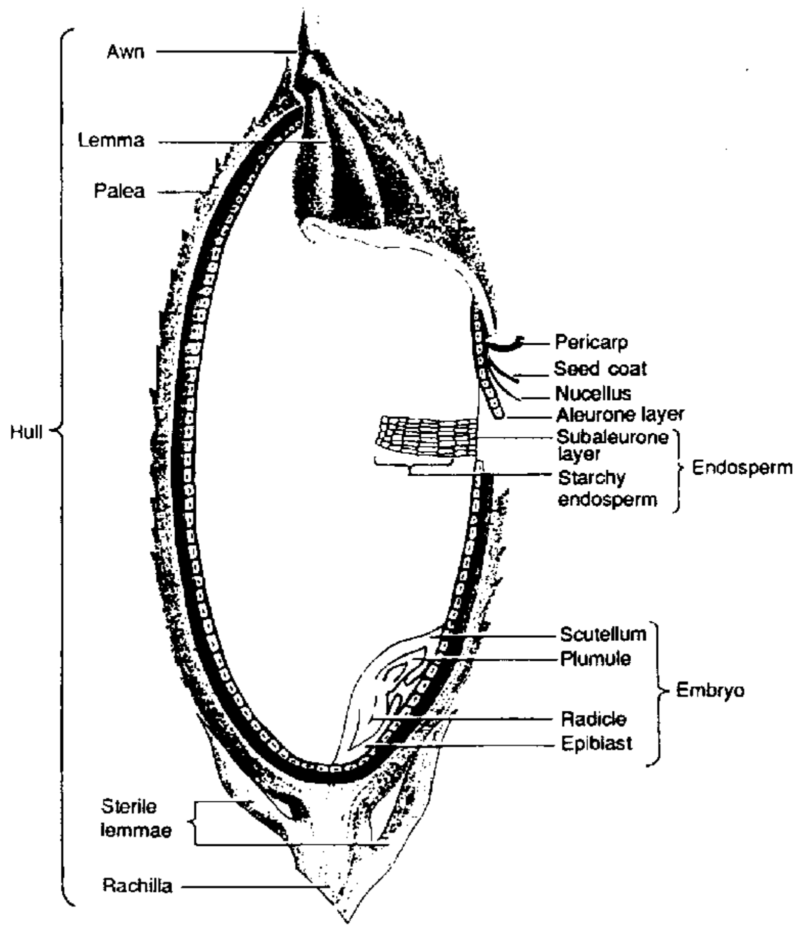



*Figure 1. General structure of a rice grain (Juliano, 1985)*

BR contains health promoting compounds, including dietary fiber, γ-aminobutyric acid (GABA), B-vitamins, phenolic compounds and γ-oryzanol, that are mainly located in the germ and bran layers which are removed during rice polishing and milling (1). Consumption of BR became popular in Japan in the 1970's because of the rich fiber and other nutrients contained in BR. However, this popularity did not last long due to the fact that brown rice had to be cooked in a pressure cooker and was still hard to chew and less tasty.

In Japan, people in the ancient era might have been eating soaked BR (2). PGBR was established for marketing in Japan in 1995. PGBR is different from BR in that it has undergone the process of germination; more specifically, the rice embryo is sprouted under suitable environmental conditions. Germination is a biomodification process that activates enzymes such as α-amylase, protease and lipase in the bran layer, which degrade starches, proteins and lipids respectively. As germination duration increases, the rice kernels and starch granules become weakened, thus resulting in softer, faster cooking rice with more nutrients retained. In general, brown rice can be germinated by soaking it in warm water of 35-40 $^{o}$C for 10-12 h, draining the water and keeping the rice in moist conditions for 20-24 h, and during the soaking period, changing the water every 3-4 h to prevent fermentation and to maintain consistent water temperature.

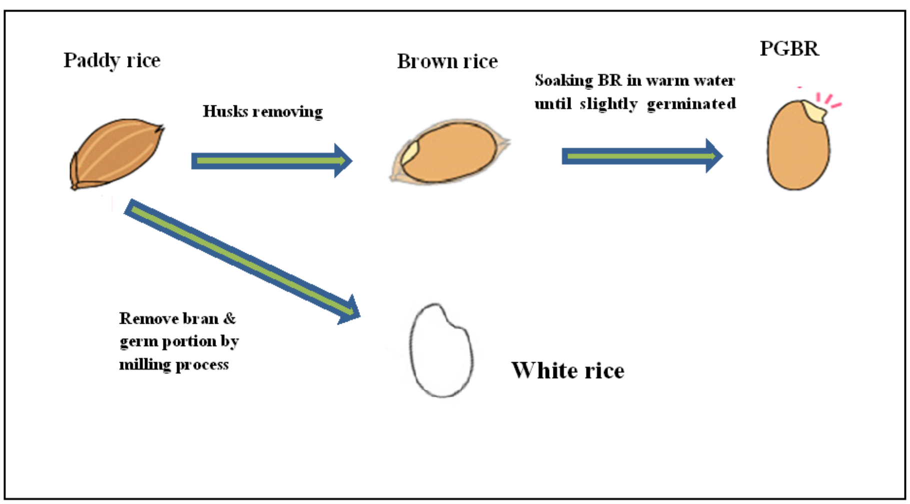


*Figure 2. Production processes of BR, WR and PGBR*

Manufactured PGBR is sold in dried form (the drying does not affect the superior nutritional value accumulated from germination), PGBR looks similar to ordinary BR. The effect of the drying process is to prolong PGBR's shelf life. PGBR overcomes the cooking problem it can be cooked in an ordinary rice cooker and is soft enough to chew, even for children. PGBR is considered as a functional food because during the process of germination, nutrients in the BR change drastically. Kayahara et al showed that not only nutrients increased but new components also released from the inner change due to germination (3). The nutrients which have increased significantly include γ-aminobutyric acid (GABA), vitamin E, dietary fiber, niacin, magnesium, vitamin B1, and vitamin B6 (3). The other nutrients that increased in PGBR were inositols (IP6), ferulic acid, tocotrienols, and γ -oryzanol (3).

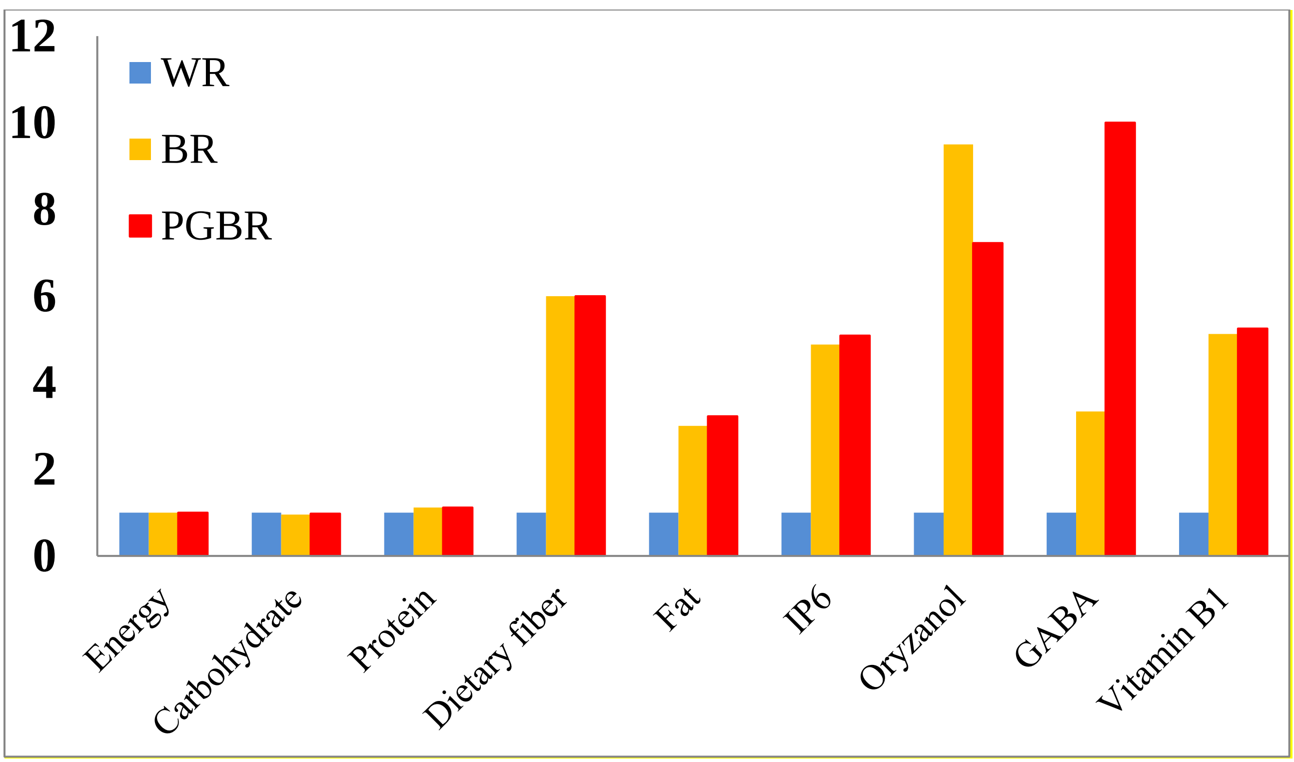



*Figure 3. Comparison of rice nutrients among WR, BR and PGBR (3)*

Serveral studies showed the results that of GABA contained in PGBR might help inhibitory process and have the ability to reduce the transmittal of stress, anxiety, grief or depression-related messages from the limbic system to the cortex. With a reduction in these messages, the emotional responses will be dampened and make a person more relaxed with a better sense of well-being (4-6). Roboon J et al showed that PGBR might have the potential to develop of the treatment for depression without adverse effects in rat models of depression (4). Shigeko et al showed that PGBR has beneficial effects on psychosomatic health and the relationship between lactation; PGBR has also attracted interest in terms of mental health and immunity (5). Mamiya et al investigated the antidepressant-like effects of PGBR and polished rice pellets in comparison with control (AIN-93G) pellets in the forced swinmming test in mice and learned helplessness paradigm in mice. The immobility time on the second day of the forced swimming test was shorter in mice fed with polished rice or PGBR pellets than in mice fed with control pellets. In the learned helplessness paradigm, the number of escape failures in mice fed with PGBR pellets was significantly smaller than that in mice fed with control pellets (6).

In Asian countries, as well as the rest of the world, the incidence of obesity has been rising rapidly. For example, the percentage (%) of adult women aged 20 and older with Body Mass Index (BMI) higher than 25 in 2014 was 48.6 in Malaysia, 39.7 in Thailand , 32.5 in Singapore, 30.9 in Taiwan, 30.6 in Indonesia, 27.4 in China, 27.2 in Korea, 20.7 in India and 17.6 in Japan (7). In Vietnam, before 1995, there was almost no obesity, the proportion of overweight people accounted for a negligible proportion in urban areas (8). The development of the economy together with rapid urbanization may predict an increase in the rate of overweight and obesity. In 2000, the results of a national survey showed that the overweight rate among women aged 15 to 49 years was 9.2% (8). The 2001-2002 National Survey also showed that the overweight rate among adult men and women was 10.1% and 13.2%, respectively (9). The proportion in urban area (Ho Chi Minh City) in 2004 was very high, among women and men was 33.6% and 31.6%, respectively (10). Overweight and obesity tend to increase in Vietnam and the prevention is really urgently required. According to a study by Vu Thi Thu Hien et al. (2013), the proportion of overweight and obesity among adults 20 years and older in Hanoi, Hue, and Ho Chi Minh Cities is 27.9% (11). For Vietnamese adults aged 25-64 years, the prevalence (%) of overweight and obesity (BMI higher than 25) was 20.3 and that of non-communicable diseases was: high blood pressure 20.3, diabetes mellitus and impaired fasting blood glucose 5.7, and high blood cholesterol 32.4 (12).

There are studies that whole grains can prevent obesity, diabetes and heart disease (13-18). BR is a whole grain; however, people prefer WR because BR itself has an unappealing taste and texture. WR is made by polishing BR and removing its surface, which makes WR softer and tastier than BR. According to a Vietnam national nutrition survey in 2009-2010, more than 66% of the energy consumption came from WR (19)

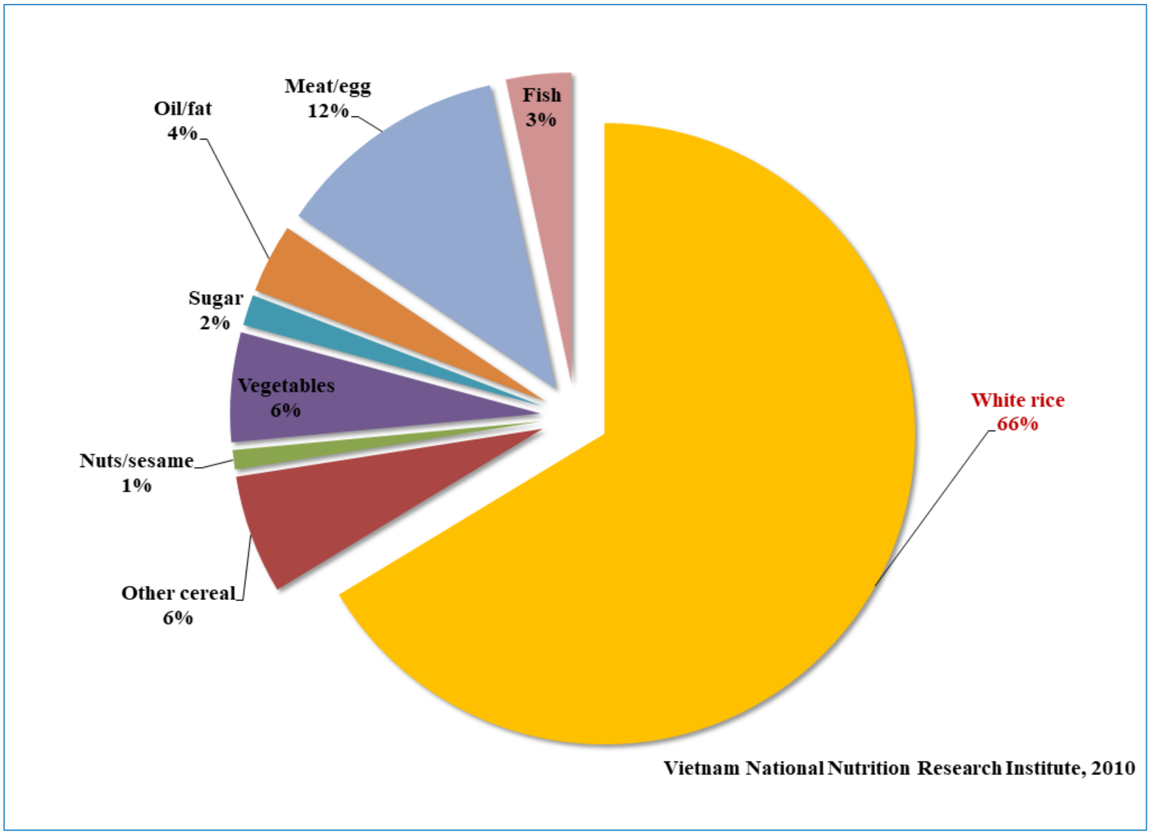


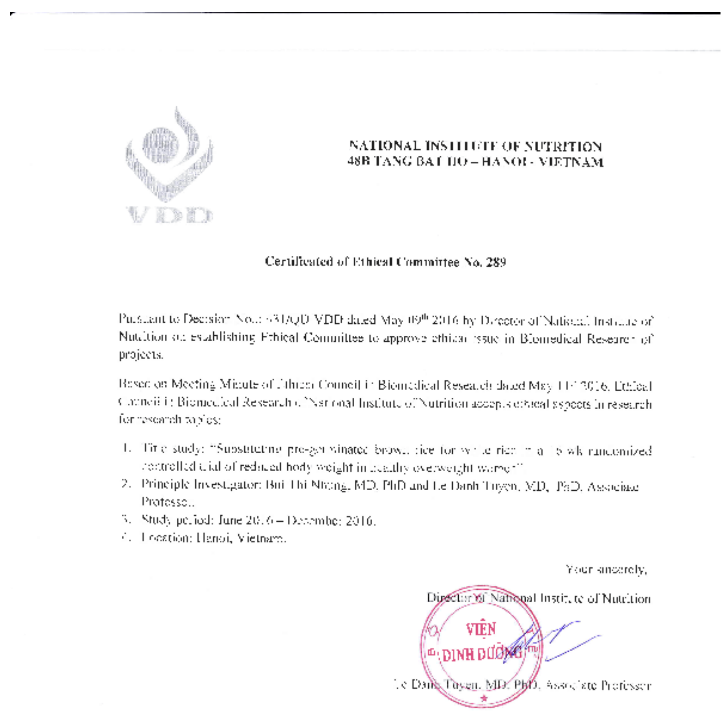

*Figure 4. Food intake in Vietnamese people in 2010*

PGBR is slightly germinated by soaking BR in water; it becomes softer in texture and has a taste close to that of WR. It maintains the various qualities of BR, for example, the fiber in BR (20, 21).We have been studying the effects of PGBR on blood glucose and lipids, mostly in DM patients (22-25). We did not observe the effect of PGBR on body weight in most of these studies, because once patients are diagnosed as DM, they are taught to reduce energy intake and body weight decreases. However, in our previous study we studied the effects on blood glucose and lipids in pre-diabetes persons without any dietary or drug management (25). Unexpectedly, we observed a decrease in body weight, which made us interested in observing the effect of PGBR on body weight in healthy overweight persons; therefore this study was conducted.

## II. MATERIALS AND METHODS

### 1 Ethical committee:

The study protocol was approved by the Scientific and Ethical Committee of the National Institute of Nutrition, Hanoi, Vietnam.



NATIONAL INSTITUTE OF NUTRITION
48B TANG BAT HO – HANOI - VIETNAM

**Certificated of Ethical Committee No. 289**

Pursuant to Decision No.: [illegible]31/QD-VDD dated May 09th 2016 by Director of National Institute of Nutrition on establishing Ethical Committee to approve ethical issue in Biomedical Research of projects.

Based on Meeting Minute of Ethical Council in Biomedical Research dated May 11th 2016, Ethical Council in Biomedical Research of National Institute of Nutrition accepts ethical aspects in research for research topics:

1. Title study: "Substituting pre-germinated brown rice for white rice in a 16 wk randomized controlled trial of reduced body weight in healthy overweight women"
2. Principle Investigator: Bui Thi Nhung, MD, PhD and Le Danh Tuyen, MD, PhD, Associate Professor.
3. Study period: June 2016 – December 2016.
4. Location: Hanoi, Vietnam.

Your sincerely,

Director of National Institute of Nutrition



Le Danh Tuyen, MD, PhD, Associate Professor

*Picture 1. Ethical committee document*

### 2 Hypothesis of this study:

"PGBR is effective in reducing overweight", was obtained by our previous studies observing the effects of PGBR on glycemic control of diabetic patients. This study was conducted to confirm the hypothesis.

**3 Study design:**

The study was a randomized control trial

**4 Sample size:**

The formula for calculating sample size was based on the average different between pre- and post-intervention indicators as below (25):

$$n = \frac{2C}{(ES)^2}$$

n: sample size

C is constant number calculated by C= $(Z_{\alpha/2} + Z_{\beta})^2$

In this study, we predefined a statistical significance level of α=0.05 then $Z_{\alpha/2}$ =1.96 and β=0.2 (power=0.8) then $Z_{\beta}$ = 0.84

then C= $(1.96 + 0.84)^2 = 7.84$

ES is Influence coefficient (abbreviated ES)

ES= $(\mu_1-\mu_2)/\sigma$ with

$(\mu_1-\mu_2)$ = 4 (kg) of diference body weight of PGBR group between final and baseline (25)

σ is fluctuation standard deviation (SD) of PGBR group at final intervention (4 month) of our previous study: 5.8 (kg) (25)

So

$$n = \frac{2(Z_{\alpha/2} + Z_{\beta})^2 \text{ x } \sigma^2}{(\mu_1 - \mu_2)^2}$$

$$n = \frac{2(1.96 + 0.84)^2 \text{ x } 5.8^2}{(4)^2}$$

$$n = 33$$

From this formula we calculated for 33 subjects in 1 group.

Dropout rate about 10% → So we selected 36 subjects for 1 group.

→ We selected in total 72 subjects.

**5. Intervention period:**

16 weeks (same as previous intervention in Pre-diabetic women was 4 months) (25).

**6. Subjects:**

***6.1 Standard for selecting subjects:***

*Criteria:*

- Women with age from 30y to 65y
- 23 $kg/m^2 \leq$ BMI $\leq$ 35 $kg/m^2$

*Exclusive criteria:*

– Those who were currently pregnant or had plans for pregnancy during the study period (by interview)

– Who were currently suffering from serious diseases such as: diabetes, kidney, mental, hepatic (by medical history).

– Who were using or had plans for weight loss therapy during the study period.

– Who were using or planning to use weight loss supplements or medicine during the study period.

– Who were eating brown rice or PGBR.

***6.2 Selecting subjects:***

Step 1: We came to a suburban medical center in Hanoi for recruiting the subjects for the study. We asked suburban medical center staff to help to publicize the clinical study announcement. The criteria and exclusive criteria were described in the announcement.

Step 2: More than 500 women wanted to join the study; a total of 473 women joined on the day of the screening test.

Step 3: We measured height, body weight and asked medical history, food habits (for PGBR or BR intake or not).

Step 4: Total of 244 women did not meet the requirements and 229 women met the criteria. After that 138 women declined to participate and 19 women dropped out for other reasons. Finally 72 women were participants in the study.

Step 5: A total of 72 women were divided randomly by matched pair by ages, body weight into a PGBR group (n=36) and a WR group (n=36).

Step 6: All participants in the PGBR group were instructed to use PGBR as their staple food for 16-week, and all participants in WR group were instructed to use WR as their staple food for 16-week.

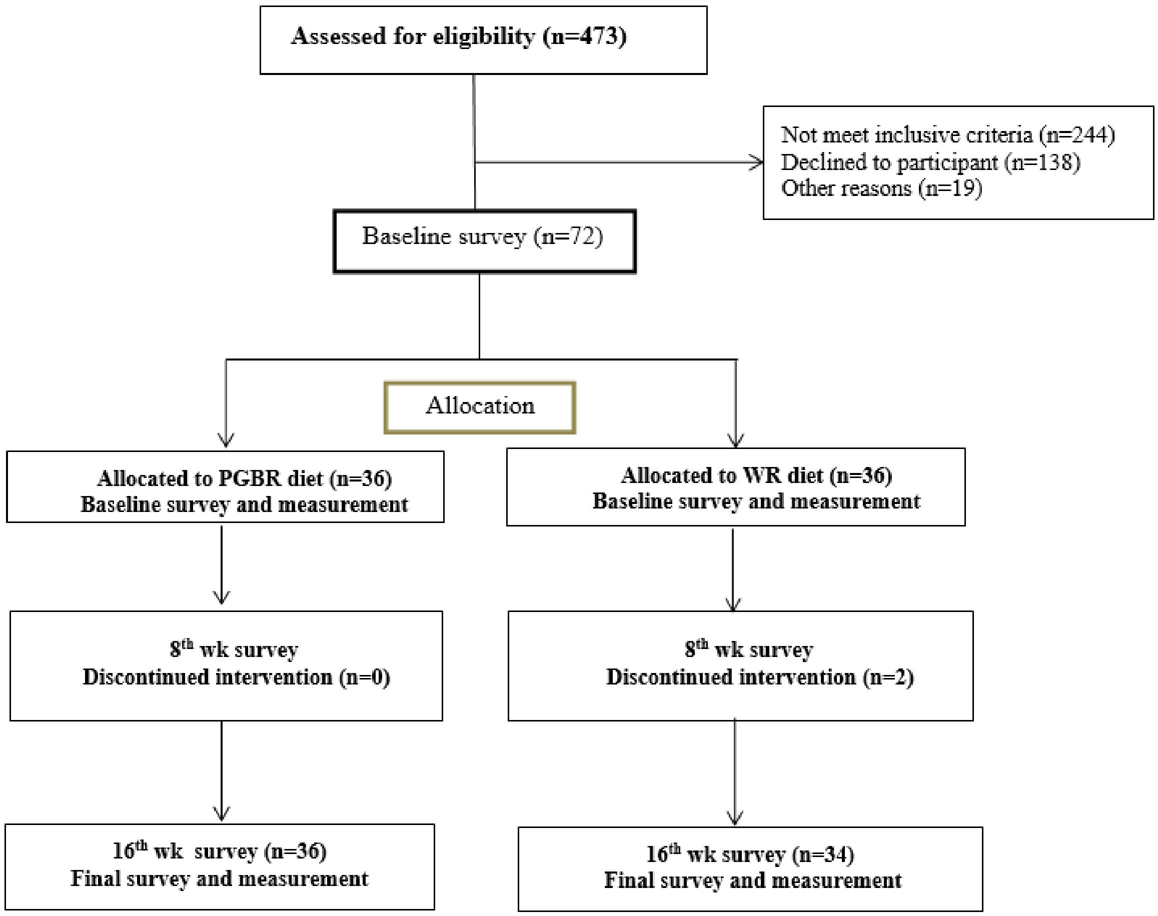



*Figure 5. Flow chart of the study*

## 7. Trial foods:

Both PGBR and WR samples were made from the same Japonica rice variety named Hoshinoyume, and obtained from Hokkaido, Japan (FANCL Tokyo, Japan). All participants were provided aseptic packaged boiled PGBR and WR. They were about 160g (about 220 kcal) which can be distributed at normal temperature and is edible after heating in a microwave oven for about 2 minutes or in boiling water for about 15 minutes.

**8. Collecting data:**

Throughout the intervention period of 16 weeks, subjects were instructed to consume either WR or PGBR exclusively as a staple food. Anthropometric measurements, nutrition survey, physical activity and blood biochemical examinations were conducted at the beginning (baseline) and at the end of the study (final). Anthropometric measurements, nutrition survey and physical activity were conducted at the midpoint (8 weeks following baseline).

***8.1 Anthropometric indicators:*** at baseline, 8 weeks and 16 weeks

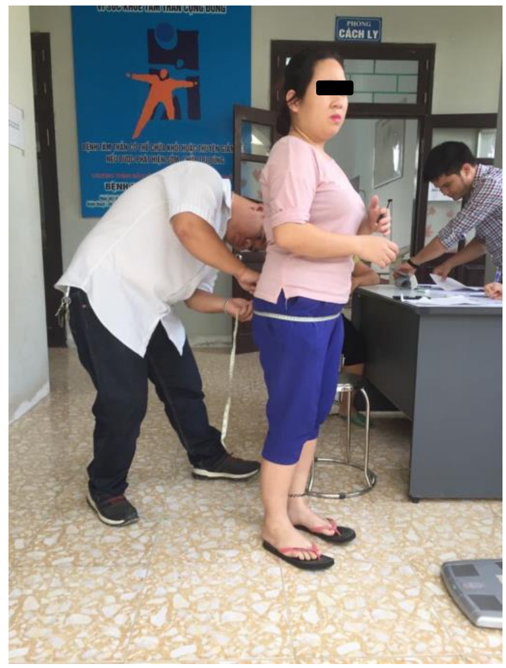
①Body weight measurement: We used electronic scales OMRON HBF-351, Kyoto, Japan. Subjects stood on the center of weight scale platform and were weighed with thin clothes, shoes and sandals removed and after fasting. The result is recorded to the nearest 0.1 kg.

*Picture 2. Measurement of body weight*

②Body height: a wooden stadiometer was used to measure the body height. The subject stands erect on the floor board barefoot and with back to the vertical backboard of the stadiometer. The weight of the subject is evenly distributed on both feet. The heels of the feet are placed together with both heels touching the base of the vertical board. The feet are pointed slightly outward at a 60 degree angle. The buttocks, scapulae, and head are positioned in contact with the vertical backboard. The results are read to record the subject`s height in centimeters with an accuracy of 0.1cm. BMI was calculated as weight (kg) divided by the square of height ($m^2$).

*Picture 3. Wooden stadiometer*

③Waist and hip circumference were measured, the result is recorded in centimeters to one decimal place. The waist circumference corresponds to the midpoint of the end of the ribs with the upper edge of the iliac crest along the median armpit. Buttocks are measured at fullest part of buttock. Subject stands in a relaxed position, with both hands hanging, the measurements in the horizontal plane.



*Picture 4. Measurement of body waist and hip*

④Body fat percentage: we used electronic scales OMRON (HBF-212b, Kyoto, Japan). We used a method called bioelectrical impedance analysis (BIA). BIA involves passing a very weak electrical current through the body to measure its resistance to the current. The electrical signal passes quickly through water that present in hydrated muscle tissue but meets resistance when it hits fat tissue. This resistance, known as impedance, is measured and input is the body fat percentage.


*Picture 5. OMRON HBF-212b*

⑤Blood pressure: we used a standardized automated sphygmomanometer (Omron HEM-6113, Tokyo, Japan). The Omron HEM-6113 device is an automatic oscillometric device for measuring radial blood pressure at the wrist level. This device uses automatic inflation by pump and automatic rapid deflation. It measures a blood pressure range of 1-299 mmHg. The device can be used for wrist cicumferences of 13.5-21.5 cm. All subjects measured blood pressured after 10 minutes of resting in seated position.


*Picture 6. Blood pressure measurement*

***8.2 Nutrition survery:*** at baseline, 8 weeks, and 16 weeks

①We used a 24h dietary recall for 3 non consecutive days (2 weekend days and 1 weekday). We used a photo book (including food intake and bowl size) as a support tool. The dietitian asked all the food that subjects consumed during breakfast, lunch, dinner and also snacks.


*Picture 7. Photo book*

②Each participant was interviewed by a skilled dietitian from the National Institute of Nutrition, Hanoi, Vietnam. Energy, carbohydrate, lipid, and dietary fiber intake were calculated based on the Vietnamese Food Composition Table 2007 (26).

*Picture 8. Nutrition interview*

③Physical activity at baseline, 8-week and 16-week*:* We used a Pedometer (Omron, Active style pro HJA-350 IT). Subjects were instructed by investigators on how to use the machine and tracking paper. Subjects wore a pedometer for five consecutive days, removing it only during a shower and when they went to bed. The average of the number of steps of the 3 middle days was used to evaluate.


*Picture 9. Pedometer*

***8.3 Blood collection***

Blood collection was conducted before the beginning of the study (baseline) and at the end of the study (final). Subjects were asked to fast for at least 10 hours before taking intravenous fasting blood samples in early morning. With aseptic precautions, each participant was subjected to a 6mL blood withdrawal and serum was isolated and kept at -80$^{o}$C until analysis. Blood glucose was measured with the use of an enzyme-couple kinetic assay. Serum total cholesterol and triacylglycerol were measured by the enzymatic method. Serum HDL-cholesterol and LDL-cholesterol were measured by the enzymatic and direct methods. All measurements were conducted by AU480 analyzer-Beckman coulter-USA at the laboratory of the National Institute of Nutrition, Hanoi, Vietnam.


*Picture 10. Blood collection*

***8.4 Acceptability:***

Overall taste, softness and stickiness were evaluated by scores from 1 to 3 (3: good; 2: moderate; 1: poor).

***8.5 Statistical methods*:**

Data were analyzed by using JMP version 11 (SAS Institute Inc., Cary, NC). Values are reported as means ± standard deviations (SD). Quantitative variables were checked for normal distribution and compared by the Student's *t*-test, *p*-values of less than 0.05 (with 2-sided) were considered statistically significant for all the analyses. Baseline characteristics of the 2 groups were compared using Student's *t*-test. Within-group differences were compared using the paired Student's *t*-test.

## III, RESULTS

### 1. Baseline characteristic of participants*:*

The 72 enrolled participants were randomly assigned to the PGBR group (n=36) or the WR group (n=36). A total of 70 participants completed the study (2 participants in the WR group discontinued intervention due to personal reasons). Table 1 shows baseline characteristics of the study population. There was no significant difference in age (*p* = 0.86), body height (*p* = 0.80), body weight (*p* = 0.55), body fat percentage (*p* = 0.71), waist circumference (*p* = 0.55), hip circumference (*p* = 0.90), systolic blood pressure (*p* = 0.06), diastolic blood pressure (*p* = 0.94), total cholesterol (*p* = 0.48), LDL-cholesterol (*p* = 0.68), HDL-cholesterol (*p* = 0.06), triacylglycerol (*p* = 0.66), or blood glucose (*p* = 0.16) between the PGBR and WR groups at baseline.

**Table 1. General characteristics of study at baseline**

| | PGBR (n=36) | | WR (n=34) | | P-values |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Age (year) | 43.3 | 7.0 | 43.6 | 7.7 | 0.81 |
| Height (cm) | 152.6 | 4.9 | 152.3 | 5.2 | 0.83 |
| Weight (kg) | 63.3 | 6.6 | 64.4 | 8.7 | 0.53 |
| BMI (kg/m$^2$) | 27.2 | 2.5 | 27.7 | 3.6 | 0.61 |
| Body fat (%) | 38.3 | 3.2 | 38.6 | 4.0 | 0.66 |
| Waist circumference (cm) | 87.3 | 6.0 | 88.2 | 7.3 | 0.61 |
| Hip circumference (cm) | 99.4 | 5.1 | 99.2 | 6.0 | 0.94 |
| Systolic blood pressure (mmHg) | 127.4 | 10.8 | 122.8 | 9.0 | 0.09 |
| Diastolic blood pressure (mmHg) | 79.6 | 7.3 | 81.5 | 8.0 | 0.84 |
| Total cholesterol (mg/dL) | 204.6 | 42.9 | 199.0 | 16.5 | 0.48 |
| LDL cholesterol (mg/dL) | 132.8 | 46.1 | 128.9 | 29.4 | 0.46 |
| HDL cholesterol (mg/dL) | 47.7 | 10.2 | 43.6 | 6.7 | 0.08 |
| Triacylglycerol (mg/dL) | 170.9 | 60.2 | 170.0 | 85.1 | 0.73 |
| Blood glucose (mg/mL) | 94.8 | 7.2 | 96.9 | 4.6 | 0.28 |

All values are means and standard deviations

P values obtain from unpaired t-test between PGBR and WR groups

**2. Change of body weight and body composition and blood pressure*:***

Table 2 shows that the body weight and BMI in the PGBR group decreased from 63.3 ± 6.6 kg and 27.2 ± 2.5 at baseline to 62.1 ± 6.5 kg ($p < 0.001$) and 26.6 ($p < 0.001$) at 8-week and 61.2 ± 6.5 kg ($p < 0.001$) and 26.3 ± 2.5 ($p < 0.001$) at 16-week, while those in the WR group were not significantly different.

In addition, body fat percentage and waist and hip circumferences decreased significantly from 38.3 ± 3.2 %, 87.3±6 cm and 99.4 ± 5.1 cm at baseline to 37 ± 2.9 % (p < 0.001), 84.6 ± 6.1 cm (p < 0.001) and 97.8 cm ($p < 0.001$) at 8-week, and to 35.3 ± 2.2 % ($p < 0.001$), 83.7 ± 5.8 cm ($p < 0.001$) and 97.6 cm ($p < 0.001$) at 16-week in the PGBR group, while only waist circumference in the WR group decreased significantly from 88.2 ± 7.3 cm at baseline to 86.5 ± 7.1 cm ($p < 0.05$) at 16-week. In the PGBR group there was a slight decrease in systolic blood pressure (mmHg) from 127.4 ± 10.8 at baseline to 123.6 ± 10 ($p < 0.05$) at 8-week and 119.8 ± 12.1 ($p < 0.001$) at 16-week but in the WR group there was a slight increase from 79.6 ± 7.3 at baseline to 82 ± 9.1 ($p < 0.05$) at 8-week and 81.7 ± 8 ($p < 0.05$) at 16-week. However, mean values of both systolic blood pressure and diastolic blood pressure in the PGBR group were within normal range. The others parameters in table 2 were not significantly different in comparison with baseline data.

Table 2. Change in anthropometric parameters and blood pressure

| | PGBR (n=36) | | | | | | | | | White rice (n=34) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | | | 8-wk | | | 16-wk | | | Baseline | | | 8-wk | | | 16-wk | | |
| | Mean | ± | SD | Mean | ± | SD | Mean | ± | SD | Mean | ± | SD | Mean | ± | SD | Mean | ± | SD |
| Weight (kg) | 63.3 | ± | 6.6 | 62.1 | ± | 6.5** | 61.2 | ± | 6.5** | 64.4 | ± | 8.7 | 64.4 | ± | 8.8 | 63.8 | ± | 9.0 |
| BMI ($kg/m^2$) | 27.2 | ± | 2.5 | 26.6 | ± | 2.5** | 26.3 | ± | 2.5** | 27.7 | ± | 3.3 | 27.7 | ± | 3.4 | 27.5 | ± | 3.4 |
| Body fat (%) | 38.3 | ± | 3.2 | 37.0 | ± | 2.9** | 35.3 | ± | 2.2** | 38.2 | ± | 4.0 | 38.6 | ± | 4.0 | 38.0 | ± | 4.2 |
| Waist circumference (cm) | 87.3 | ± | 6.0 | 84.6 | ± | 6.1** | 83.7 | ± | 5.8** | 88.2 | ± | 7.3 | 88.0 | ± | 6.8 | 86.5 | ± | 7.1* |
| Hip circumference (cm) | 99.4 | ± | 5.1 | 97.8 | ± | 4.9** | 97.6 | ± | 5.0** | 99.2 | ± | 6.0 | 99.3 | ± | 5.9 | 98.8 | ± | 6.1 |
| Systolic blood pressure (mmHg) | 127.4 | ± | 10.8 | 123.6 | ± | 10.0* | 119.8 | ± | 12.1** | 122.8 | ± | 9.0 | 124.0 | ± | 13.1 | 120.9 | ± | 10.1 |
| Diastolic blood pressure (mmHg) | 79.6 | ± | 7.3 | 82.0 | ± | 9.1* | 81.7 | ± | 8.0* | 79.5 | ± | 6.0 | 81.5 | ± | 8.0 | 80.1 | ± | 7.8 |

All values are means and standard deviations

*, ** Significantly different compared to baseline by paired *t*-test; $p<0.05$ and $p<0.001$, respectively

### 3. Blood biochemical parameters:

The change in blood parameters are indicated in table 3. Concentrations of blood parameters (mg/dL) in the PGBR group at baseline and 16-week decreased; total cholesterol from 204.6 ± 42.9 to 182.1 ± 31.6 ($p < 0.001$), LDL-cholesterol from 132.8 ± 46.1 to 108.4 ± 28.8 ($p < 0.05$), triacylglycerol from 170.9 ± 60.2 to 135.2 ± 71.7, and glucose from 94.8 ± 7.2 ($p < 0.05$) but in the WR group none of these changed. HDL-cholesterol of both the PGBR and WR groups increased significantly at 16-week in comparison with baseline ($p < 0.05$).

Table 3. Blood parameters of PGBR and WR groups at baseline and final

| | PGBR (n=36) | | | | | | WR (n=34) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | | | 16-wk | | | Baseline | | | 16-wk | | |
| | Mean | ± | SD | Mean | ± | SD | Mean | ± | SD | Mean | ± | SD |
| Total cholesterol (mg/dL) | 204.6 | ± | 42.9 | 182.1 | ± | 31.6** | 199.0 | ± | 16.5 | 205.6 | ± | 22.7 |
| LDL cholesterol (mg/dL) | 132.8 | ± | 46.1 | 108.4 | ± | 28.8* | 128.9 | ± | 29.4 | 122.5 | ± | 26.5 |
| HDL cholesterol (mg/dL) | 47.7 | ± | 10.2 | 50.7 | ± | 10.0* | 43.6 | ± | 6.7 | 47.1 | ± | 9.1* |
| Triacylglycerol (mg/dL) | 170.9 | ± | 60.2 | 135.2 | ± | 71.7* | 178.7 | ± | 86.8 | 170.0 | ± | 85.1 |
| Blood glucose (mg/mL) | 94.8 | ± | 7.2 | 90.2 | ± | 10.9* | 96.9 | ± | 4.6 | 98.7 | ± | 8.6 |

All values are means and standard deviations

*, ** Significantly different compared to baseline by paired *t*-test; p<0.05 and p<0.001, respectively

**4. Nutrition survey and physical activity*:***

Table 4 shows the energy and nutrient intakes and physical activity of the PGBR and WR groups at baseline, 8-week, and 16-week. In the PGBR group, energy, protein and carbohydrate at 16-week decreased significantly in comparison with baseline ($p < 0.05$). Dietary fiber intake of the PGBR group at baseline was 6.5 ± 1.7 g and increased to 12.6 ± 2.6 g ($p < 0.001$) at 8-week and 14.0 ± 3.6 g ($p < 0.001$) at 16-week. In the WR group, none of these items changed significantly.

Table 4. Nutrient intakes and physical activity

| | PGBR (n=36) | | | | | | | | | WR (n=34) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | | | 8-wk | | | 16-wk | | | Baseline | | | 8-wk | | | 16-wk | | |
| | Mean | ± | SD | Mean | ± | SD | Mean | ± | SD | Mean | ± | SD | Mean | ± | SD | Mean | ± | SD |
| Energy (Kcal) | 1911.7 | ± | 271.8 | 1857.2 | ± | 218.0 | 1803.1 | ± | 211.5* | 1901.9 | ± | 186.9 | 1882.8 | ± | 190.2 | 1878.9 | ± | 205.6 |
| Protein (g) | 69.5 | ± | 11.5 | 69.7 | ± | 9.7 | 66.3 | ± | 12.0* | 70.4 | ± | 12.0 | 68.7 | ± | 10.0 | 69.2 | ± | 8.1 |
| Lipid (g) | 46.0 | ± | 8.4 | 44.8 | ± | 8.1 | 46.4 | ± | 7.4 | 41.5 | ± | 8.1 | 40.5 | ± | 6.5 | 42.5 | ± | 6.8 |
| Carbohydrate (g) | 304.9 | ± | 53.3 | 293.9 | ± | 45.7 | 280.1 | ± | 35.1* | 311.8 | ± | 41.7 | 310.9 | ± | 36.7 | 304.8 | ± | 39.7 |
| Fiber (g) | 6.5 | ± | 1.7 | 12.6 | ± | 2.8** | 14.0 | ± | 3.6** | 6.5 | ± | 2.6 | 6.5 | ± | 3.3 | 6.8 | ± | 1.8 |
| Physical activity (steps) | 6978 | ± | 2821 | 7498 | ± | 3732 | 7085 | ± | 3514.1 | 6869 | ± | 2523 | 7268 | ± | 3540 | 6886 | ± | 2100 |

All values are means and standard deviations

*, ** Significantly different compared to baseline by paired *t*-test; $p<0.05$ and $p<0.001$, respectively

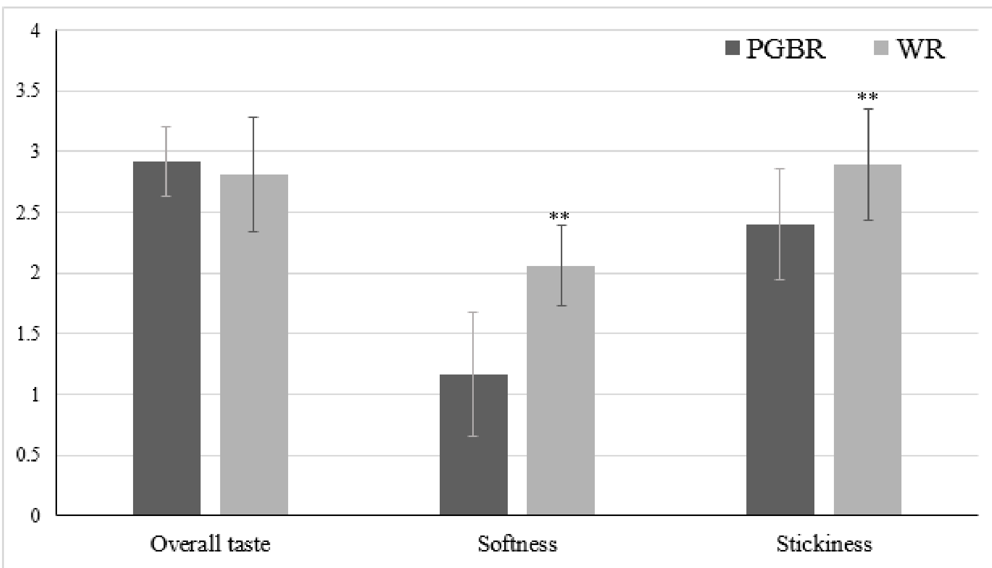



Figure 6. Acceptability of PGBR (3: good; 2: moderate; 1: poor)

**Statistically different ($p<0.01$)

Fig. 6 shows the comparison of scores of overall taste, softness and stickiness between PGBR and WR. They were evaluated by scores from 1 to 3 (3 good; 2 moderate; 1 poor). WR was softer and more sticky than PGBR ($p<0.05$) but the overall taste was similar.

## IV, DISCUSSION

The present 16-week randomized, controlled trial suggests that replacing WR with PGBR might have beneficial effects for controlling body weight in healthy overweight and obese women. The main focus of the study was reduction of body weight with PGBR; body weight (kg) of the PGBR group decreased from 63.3 ± 6.6 to 61.2 ± 6.5 (2.1 kg decrease in 16-week), while the WR group changed only slightly, from 64.4 ± 8.7 to 63.8 ± 9.0 (only 0.6 kg decrease). We also observed a decrease in waist and hip circumferences and beneficial effects in blood lipid profiles. It is well-known that body weight is controlled by energy balance: energy IN (food intake) and energy OUT (physical activity). We measured physical activity by pedometer and did not observe any difference at baseline, 8-week, and 16-week in either group (Table 4). From these data on total energy intake and physical activity (steps), it might be inferred that body weight in the PGBR group may have decreased from reducing their energy balance.

However, in our previous study of DM patients who had received nutrition education from doctors or dietitians (22-24), we did not observe a reduction of body weight in the PGBR group except for one study conducted in pre-DM patients without nutrition education (25). In the present study, we selected healthy overweight subjects without any health problems and confirmed clearly that PGBR was useful in reducing body weight.

In this study all the WR and PGBR was supplied by us for the whole study period (4 months). Rice is the subjects' staple food and subjects ate rice at least twice over 3 meal times (breakfast, lunch and dinner). Both the WR and PGBR were same strain of rice produced in the same area and packets of about 160g (250-300kcal) are available in the market. Packets could be stored at normal temperatures and made edible by heating in a microwave oven for about 2 minutes or in boiling water for about 15 minutes. The use of this pre-packaged rice made the study easier for subjects as well as for the researchers and dropouts were limited to only a few. Researchers were not concerned with rice for other family members.

With regard to the decreased energy intake in the PGBR group, we had to determine whether the taste of PGBR was acceptable to the subjects. People prefer WR to BR, because WR is softer and tastier than BR. WR is made by polishing BR and removing its surface. PGBR is slightly germinated by soaking BR in water. In the process, the BR skin is broken apart and becomes soft. From our sensory test, we found that although the PGBR was a little harder and less sticky than WR, the taste was evaluated as high as WR. From these results we concluded that the decrease of energy intake in the PGBR group was not due to its taste.

Dietary fiber might affect body weight through multiple pathways, including through modulation of insulin secretion and control of satiety (27-29). In our study, the intake of dietary fiber (g/day) in the PGBR group was 6.5 ± 1.7 at the baseline, 12.6 ± 2.8 at 8-week and 14.0 ± 3.6 at 16-week and much higher than that at baseline. There was no change in the WR group being 6.5 ± 2.6, 6.5 ± 3.3 and 6.8 ± 1.8 at baseline, 8-week and 14.0 at 16-week, respectively.

Many studies have investigated the relation of low glycemic (GI) index foods and body weight. PGBR contains higher dietary fiber and has a lower GI than WR (22). Previous studies showed that rapid absorption of glucose after consumption of high GI foods could lead to sharp rises in blood glucose and insulin levels; thus, glucose enters body tissues, inhibits lipolysis and induces lipogenesis and obesity. (30, 31)

Increased fiber makes the subjects feel full for a longer time, which might be associated with reduced hunger or increased satiety, leading to reduced total energy intake (32-35). Birketvedt et al (36) found that the addition of dietary fiber to a low-calorie diet significantly improved weight loss, with the placebo group losing 5.8 kg and the fiber-supplemented group losing 8.0 kg in overweight subjects. With a longer chewing time and slower digestion and absorption, nutrient receptors in the gastrointestinal tract are stimulated for a longer time; this will prolong feedback to the satiety center in the brain and reduce energy intake (32, 33). However, fiber alone is not enough to explain the effect of PGBR on body weight, because PGBR has various functional ingredients different from WR (21) and we do not know their possible effects on body weight. PGBR is richer than WR in vitamins, minerals and dietary fiber, γ-oryzanol, and ferulic acid and acylated steryl glucosides.

In PGBR, GABA concentration is 5-8 times higher than that of WR (22). Sandoval-Salazar C et al. showed that a high fat diet decreases GABA levels in the frontal cortex and hippocampus of rats, which likely disrupts the GABAergic inhibitory processes, underlying feeding behavior (37). Furthermore, at the end of study, the high fat diet decreased GABA levels group had a significant increase in body weight compared with the standard diet group ($p=0.0004$) (37). GABA has been proposed to play a key role in the cognitive choice of selecting the type, quantity and quality of food by regulating the transmission of signals between neurons in brain circuits (38). GABA is the major inhibitory neurotransmitter in the mammalian brain and has been implicated in controlling excitability, the processing of information, plasticity, and the synchronization of neuronal activity (39). Additionally, the involvement of GABA in eating behavior has been supported in experiments using rodent models and GABA receptor agonists and antagonists (40). A study in rats suggests that obesity may be associated with decreased GABA production due to a disturbance in the GABA-glutamate-glutamine cycle in the hippocampus (41). Research has implicated GABA in the complex neurological processes that control fear and anxiety, and also in those related to the control of appetite and metabolism (37-

41). But direct proof of the role GABA plays in weight control has been elusive in part for the lack of better methodology to precisely control GABA production by brain cells.

In conclusion, the present study shows that replacing WR with PGBR for a 16-week intake could reduce body weight in healthy overweight women. From these findings, the rapid increase in overweight and obesity in Vietnam could be controlled by the use of PGBR.

## Authorship

This thesis based on the article “Substituting Pre-germinated Brown Rice for White Rice Reduced Body Weight in Healthy Overweight Vietnamese Women” by Linh VA, Nhung BT, Tuyen LD, Anh NDV, Ito Y, Yui K, Yamamoto S. 2019 Asian Journal of Dietics.

The contribution of Linh VA to this article:

- Concept and method development
- Literature research
- Data preparation
- Calculation
- Paper writing

The other authors declare no conflict of interests regarding the publication of this article.

## ACKNOWLEDGMENTS

The authors are grateful to all participants and the staff members of the National Institute of Nutrition, Hanoi, and local public health officials for collaborating in the study. This study was supported by Jumonji University and the US-Japan Medical Science Program. We would like to thank Andrew R. Durkin, Professor Emeritus of Indiana University, Bloomington, IN, USA, for his careful editing of the English of this article.

## REFERENCES

1) Monks JLF, Vanier NL, Casaril J, Berto RM, de Oliveira M, Gomes CB, et al. Effects of milling on proximate composition, folic acid, fatty acids and technological properties of rice. J Food Compos Anal. 2013 Jun;30(2):73–9.

2) Kayahara H, Takamura M. Surprising live germinated brown rice. In: Shougakukan-Square. Tokyo; 2003.

3) Kayahara H, Tsukahara K, Tatai T. Flavor, health and nutritional quality of pre-germinated brown rice. In: Spanier AM, Shahidi F, Parliment TH, Mussinan C, Ho C-T, Contis ET, editors. Food Flavors and Chemistry: Advances of the New Millennium. The Royal Society of Chemistry; 2001. p. 546–51.

4) Roboon J, Nudmamud-Thanoi S, Thanoi S. Recovery effect of pre-germinated brown rice on the alteration of sperm quality, testicular structure and androgen receptor expression in rat model of depression. Andrologia. 2017 Feb 1;49(1).

5) Sakamoto S, Hayashi T, Hayashi K, Murai F, Hori M, Kimoto K, et al. Pre-germinated brown rice could enhance maternal mental health and immunity during lactation. Eur J Nutr. 2007 Oct;46(7):391–6.

6) Mamiya T, Kise M, Morikawa K, Aoto H, Ukai M, Noda Y. Effects of pre-germinated brown rice on depression-like behavior in mice. Pharmacol Biochem Behav. 2007 Jan;86(1):62–7.

7) Thailand Overweight prevalence second in Southeast Asia – Asean, Featured, Health [Internet]. [cited 2019 Aug 15]. Available from: https://www.thailand-business-

news.com/asean/49065-thailand-ranks-second-asean-prevalence-obesity-mcot-net.html

8) Nguyen TT, Hoang M V. Non-communicable diseases, food and nutrition in Vietnam from 1975 to 2015: The burden and national response. Vol. 27, Asia Pacific Journal of Clinical Nutrition. HEC Press; 2018. p. 19–28.

9) Ministry of Heath-National Institute of Nutrition. National General Nutrition Survey 2000. Hanoi: Medical Publishing House; 2003.

10) Ministry of Heath-Vietnam Statistic Committee. Report on National Medical Survey in 2001-2002. Hanoi: Medical Publishing House; 2003.

11) Cuong TQ, Dibley MJ, Bowe S, Hanh TTM, Loan TTH. Obesity in adults: An emerging problem in urban areas of Ho Chi Minh City, Vietnam. Eur J Clin Nutr. 2007 May;61(5):673–81.

12) Hien VTT, el al. The prevalence of overweight and obesity in adults aged 20 and older in Hanoi, Thua Thien Hue and Ho Chi Minh City. J Nutr Food. 2013;9(3):86–92.

13) Liu S, Willett WC, Manson JAE, Hu FB, Rosner B, Colditz G. Relation between changes in intakes of dietary fiber and grain products and changes in weight and development of obesity among middle-aged women. Am J Clin Nutr. 2003 Nov;78(5):920–7.

14) Bazzano LA, Song Y, Bubes V, Good CK, Manson JE, Liu S. Dietary intake of whole and refined grain breakfast cereals and weight gain in men. Obes Res. 2005;13(11):1952–60.

15) Sahyoun NR, Jacques PF, Zhang XL, Juan W, McKeown NM. Whole-grain intake is inversely associated with the metabolic syndrome and mortality in older adults. Am J Clin Nutr. 2006 Jan 1;83(1):124–31.

16) McKeown NM, Yoshida M, Shea MK, Jacques PF, Lichtenstein AH, Rogers G, et al. Whole-Grain Intake and Cereal Fiber Are Associated with Lower Abdominal Adiposity in Older Adults. J Nutr. 2009 Oct 1;139(10):1950–5.

17) Shimabukuro M, Higa M, Kinjo R, Yamakawa K, Tanaka H, Kozuka C, et al. Effects of the brown rice diet on visceral obesity and endothelial function: The BRAVO study. Br J Nutr. 2014 Jan 28;111(2):310–20.

18) Kondo K, Morino K, Nishio Y, Ishikado A, Arima H, Nakao K, et al. Fiber-rich diet with brown rice improves endothelial function in type 2 diabetes mellitus: A randomized controlled trial. PLoS One. 2017 Jun 1;12(6).

19) National Institute of Nutrition. National Nutrition Survey 2009-2010. Hanoi: Hanoi Medical Publisher; 2010.

20) Seki T, Nagase R, Torimitsu M, Yanagi M, Ito Y, Kise M, et al. Insoluble fiber is a major constituent responsible for lowering the post-prandial blood glucose concentration in the pre-germinated brown rice. Biol Pharm Bull. 2005 Aug;28(8):1539–41.

21) Patil SB, Khan MK. Germinated brown rice as a value added rice product: A review. Vol. 48, Journal of Food Science and Technology. 2011. p. 661–7.

22) Ito Y, Mizukuchi A, Kise M, Aoto H, Yamamoto S, Yoshihara R, et al. Postprandial blood glucose and insulin responses to pre-germinated brown rice in healthy subjects. J Med Investig. 2005 Aug;52(3–4):159–64.

23) ITO, Y. Effect of pre-germinated brown rice on postprandial blood glucose and insulin level in subjects with hyperglycemia. Jpn J Food Chem. 2005;12:80–4.

24) Hsu TF, Kise M, Wang MF, Ito Y, Yang MD, Aoto H, et al. Effects of pre-germinated brown rice on blood glucose and lipid levels in free-living patients with impaired fasting glucose or type 2 diabetes. J Nutr Sci Vitaminol (Tokyo). 2008 Apr;54(2):163–8.

25) Bui TN, Le Hop T, Nguyen DH, Tran QB, Nguyen TL, Le DT, et al. Pre-germinated brown rice reduced both blood glucose concentration and body weight in vietnamese women with impaired glucose tolerance. J Nutr Sci Vitaminol (Tokyo). 2014;60(3):183–7.

26) National Institute of Nutrition. Vietnamese Food Composition Table. Hanoi: Hanoi Medical Publishing House; 2007.

27) Heaton KW. FOOD FIBRE AS AN OBSTACLE TO ENERGY INTAKE. Lancet. 1973 Dec 22;302(7843):1418–21.

28) Lavin JH, Wittert GA, Andrews J, Yeap B, Wishart JM, Morris HA, et al. Interaction of insulin, glucagon-like peptide 1, gastric inhibitory polypeptide, and appetite in response to intraduodenal carbohydrate. Am J Clin Nutr. 1998;68(3):591–8.

29) de Vries J, Miller PE, Verbeke K. Effects of cereal fiber on bowel function: A systematic review of intervention trials. Vol. 21, World journal of gastroenterology. 2015. p. 8952–63.

30) Pawlak DB, Bryson JM, Denyer GS, Brand-Miller JC. High Glycemic Index Starch Promotes Hypersecretion of Insulin and Higher Body Fat in Rats without Affecting Insulin Sensitivity. J Nutr. 2001 Jan 1;131(1):99–104.

31) Ludwig DS. The glycemic index: Physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. J Am Med Assoc. 2002 May 8;287(18):2414–23.

32) Wrick KL, Robertson JB, Van Soest PJ, Lewis BA, Rivers JM, Roe DA, et al. The

Influence of Dietary Fiber Source on Human Intestinal Transit and Stool Output. J Nutr. 1983 Aug 1;113(8):1464–79.

33) Andrade AM, Greene GW, Melanson KJ. Eating Slowly Led to Decreases in Energy Intake within Meals in Healthy Women. J Am Diet Assoc. 2008 Jul;108(7):1186–91.

34) Scisco JL, Muth ER, Dong Y, Hoover AW. Slowing Bite-Rate Reduces Energy Intake: An Application of the Bite Counter Device. J Am Diet Assoc. 2011 Aug;111(8):1231–5.

35) Li J, Zhang N, Hu L, Li Z, Li R, Li C, et al. Improvement in chewing activity reduces energy intake in one meal and modulates plasma gut hormone concentrations in obese and lean young Chinese men. Am J Clin Nutr. 2011 Sep 1;94(3):709–16.

36) Birketvedt GS, Aaseth J, Florholmen JR, Ryttig K. Long-term effect of fibre supplement and reduced energy intake on body weight and blood lipids in overweight subjects. Acta Medica (Hradec Kralove). 2000;43(4):129–32.

37) Sandoval-Salazar C, Ramírez-Emiliano J, Trejo-Bahena A, Oviedo-Solís CI, Solís-Ortiz MS. A high-fat diet decreases GABA concentration in the frontal cortex and hippocampus of rats. Biol Res. 2016 Jan 6;49(1).

38) Farrar AM, Font L, Pereira M, Mingote S, Bunce JG, Chrobak JJ, et al. Forebrain circuitry involved in effort-related choice: Injections of the GABAA agonist muscimol into ventral pallidum alter response allocation in food-seeking behavior. Neuroscience. 2008 Mar 18;152(2):321–30.

39) Owens DF, Kriegstein AR. Is there more to GABA than synaptic inhibition? Vol. 3, Nature Reviews Neuroscience. 2002. p. 715–27.

40) Avena NM, Bocarsly ME, Murray S, Gold MS. Effects of baclofen and naltrexone, alone and in combination, on the consumption of palatable food in male rats. Exp Clin Psychopharmacol. 2014;22(5):460–7.

41) Sickmann HM, Waagepetersen HS, Schousboe A, Benie AJ, Bouman SD. Obesity and type 2 diabetes in rats are associated with altered brain glycogen and amino-acid homeostasis. J Cereb Blood Flow Metab. 2010 Aug;30(8):1527–37.