ORIGINAL

Effects of Pre-Germinated Brown Rice on Blood Glucose Concentration of Type 2 Diabetes Mellitus Patients in Vietnam

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ABSTRACT In recent years, type 2 diabetes mellitus (DM) prevalence in Vietnam is increasing rapidly. Newly diagnosed Vietnamese DM patients were reported to have low body mass index (BMI) of around 23, and high white rice intake has been identified as one of the major causes. As a recommended staple food substitute for white rice, brown rice has the disadvantages of hard texture and unfavorable taste. These drawbacks can be compensated in the process of making pre-germinated brown rice (PGBR), by soaking BR in lukewarm water to make it slightly sprouted. Previous studies have suggested that similar to BR, PGBR is effective in modulating blood glucose and lipid concentration levels. In this study, a 4-month PGBR administration was applied to evaluate the efficiency of PGBR on HbA1c index of Vietnamese type 2 diabetics. The present results suggest that replacing WR with PGBR may be useful in modulating blood glucose levels in Vietnamese type 2 DM patients.

Keywords: PGBR; DM; HbA1c; Vietnamese

INTRODUCTION

The prevalence of type 2 diabetes mellitus (DM) is increasing worldwide at a dramatic pace. According to the World Health Organization (WHO), DM ranked 8th among 10 leading causes of death in the world, having caused 1.5 million deaths within a year of 2013 (1). Around 80% of people with diabetes reside in developing nations, where striking transformation in lifestyle, population structure and growth rates are major contributors to the wide spread of the epidemic. As reported by the International Diabetes Federation (2), the prevalence of type 2 DM in Vietnam has doubled within a decade, rising from 2.7% (2002) to 5.4% (2012). As of 2012, Vietnam was home to nearly 3.3 million DM cases, with more than 54,000 deaths by DM-related diseases (2). It is anticipated that by 2030, the number of type 2 DM cases in Vietnam will double in comparison to 2010 (3).

Although DM has been consistently associated with obesity, studies have indicated that type 2 DM develops at a lower body mass index (BMI) range among Asians as opposed to those of Western populations, and that at the same BMI, Asian populations have a higher incidence of DM than their Western counterparts (4-6). In Vietnam, various studies in the 1990s and 2000s showed that Vietnamese DM patients have low BMI of approximately 23 (7-8). The use of white rice (WR) as a staple food may serve as the major factor, since it has been demonstrated and distinguished as a high glycemic index (GI) food and a risk factor for DM (10-11).

GI was proposed by Jenkins et al in 1980 as an indicator reflecting post-prandial blood glucose response after digesting foods (12). Since then, a strong relationship between GI and DM has been observed. It is expected that a carbohydrate-rich diet accompanied by rapid glucose absorption, i.e. a diet with high GI value, is strongly associated with increased risks for diabetes (13-14). Although it may vary depending on such factors as amylose content or refining process, the average GI value of WR is generally described to be higher than that of whole wheat cereals. In particular, GI value of WR was 76±7, 62±5 for BR, 30±9 for whole wheat and 29±5 for barley kernels in an earlier meta-analysis (15). A large-scale study with more than 59,000 subjects by Nanri et al linked high WR intake with an increased risk of type 2 DM in Japanese women (16). Although WR has been validated as a high GI food and a DM risk factor, for centuries it has been the major staple food that laid the foundation of the traditional Vietnamese diet. According to the National Nutrition Survey 2009-2010, as much as 67% of total energy intake in the diet of Vietnamese people comes from white rice, despite the dramatic change in dietary habits in recent decades (17). The long tradition of consuming rice as a staple

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food makes it difficult for Asians, including the Vietnamese, to reduce rice intake.

As low GI foods, whole grains such as BR or whole wheat are often recommended to be consumed in combination with high GI staple foods in Asian style diets, namely WR and white bread, in order to restrain rapid elevation of blood glucose and control metabolic syndrome risk factors (18). Epidemiologic studies have demonstrated an inverse association between risks of metabolic syndrome and whole grain consumption. Ye et al (19) reviewed 66 papers published between 1996 and 2012 and reported a 21% decrease in DM and 21% decrease in heart diseases by the daily intake of 370g whole grains. Low GI diets have been known to exert positive effects similar to that of several anti-hyperglycemic pharmacological agents, as suggested by Brand-Miller in a previous meta-analysis (20). In recent years, significant evidence has transpired in respect of the influences of BR on blood glucose and DM risks. A cohort study by Harvard School of Public Health reviewing 3 studies on 197,228 subjects found that replacing 50g WR (equivalent to one third of a typical daily serving) with an alternative portion of BR everyday can help lower risk of type 2 DM by 16% (11).

BR is made by removing the outermost husk of the rice grain, whereas WR is made by depriving BR of its bran and germ portion. Due to the differences in processing, WR primarily consists of starch whilst BR maintains prominent nutrient contents of dietary fiber, vitamins and minerals (11, 21-22). BR however, has several problems of tough texture and unpleasant palatability, causing difficulty in digestion as well as meal preparation, especially in large quantity. In recent years, a new type of rice called pre-germinated brown rice (PGBR) has been developed and known to Vietnam. PGBR is produced by soaking BR in lukewarm water until slight germination. In PGBR, nutrient contents of BR are retained, whereas the hardness of the texture is reduced and the taste is considerably improved (23). Scientific evidence showed that the germination process also activates several bioactive components available in the rice bran like γ-aminobutyric acid (GABA), acylated steryl glycoside (ASG), or γ-oryzanols (21-23, 36). Similar to BR, PGBR is a low GI food (GI=54±5) (15).

PGBR has been reported to exert beneficial effects in preventing rapid elevation of blood glucose response and plasma insulin concentrations (21-22, 24). A previous study showed that a long-term diet with PGBR as a staple food reduced both blood glucose concentration and body weight in Vietnamese female subjects with impaired glucose tolerance (24).This study was conducted to evaluate the influence of PGBR consumption on the control of HbA1c value in DM patients under long-term anti-diabetic medication.

METHODS

Setting and study subjects

This study was designed as a parallel study in compliance with the Helsinki Declaration on Human studies. It was conducted from December 2014 to April 2015 in Nam Dinh Endocrinology Hospital of Nam Dinh province – a coastal administrative division located 90 km southeast from Hanoi, Vietnam. The population was approximately 2 million, nearly 18 per cent of which living in urban areas. The study protocol was approved by the Scientific Board and the Ethical Committee of Vietnam’s National Institute of Nutrition (NIN).

Over the course of one month, medical database of more than two hundred DM patients affiliated with Nam Dinh Endocrinology Hospital were screened for subject selection. Patients referred to insulin injection were excluded. Based on the latest health-check and blood test results (with Hemoglobin A1c index of 6.5 – 9.5), 70 individuals were invited to participate. A briefing session was organized in order to provide potential participants with thorough details of the study, as well as the prospective beneficial health impacts of whole grains and PGBR. In addition, a test meal was provided to each person to account their ability of adaptation with PGBR as a staple food. Two weeks prior to the study baseline, informed consent was obtained from each individual. In accordance with the informed consent, participants were allowed to withdraw from the study at any time and by any reason. At the end of the subject selection process, a total number of 60 participants were achieved. To minimize the drop-out rate, subjects were contacted on weekly basis to track their rice intake and health status throughout the study.

All subjects have been taking oral anti-diabetic drugs for several years. Administration involves combination of common anti-hypoglycemic agents, particularly sulfonylureas (which act by increasing insulin secretion), intestinal α-glucosidase inhibitors (which delay the digestion and absorption of carbohydrates) and thiazolidinediones (which stimulate insulin activity without inducing insulin secretion).

Study design

This is a parallel study design. From 60 participants, 30 matched pairs were created according to age, HbA1c results and physical activity intensity. Matched pairs were then randomly divided into either WR group (control group) or PGBR group (intervention group).

Throughout the intervention period of 4 months, subjects were instructed to consume either WR or PGBR exclusively as a staple food. Before the beginning (baseline), at the midpoint (two months following baseline) and at the end of the study (final), anthropometric measurements, nutrition survey, and blood biochemical examinations were conducted. Participants were guided to pursue normal activities of daily life, as well as to continue anti-diabetic medication.

PGBR was produced in Nam Dinh Province with technological support from FANCL Corp., Japan. PGBR was prepared by soaking BR in lukewarm water of around 30°C in 22 hours and dried for preservation. The rice used in this study was of Tam Thom – a fragrant, long-grain rice variety native to the Red River Delta in Northern Vietnam. PGBR was provided to subjects of the PGBR group once every two weeks. Excluding staple food, participants were instructed to continue usual diet without any alteration.

Blood collection

Blood collection was conducted before the beginning of the study (baseline), at the midpoint 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 6 mL blood withdrawal for the analyses of glucose, HbA1c, triacylglycerol (TG), total cholesterol (TC), LDL-cholesterol (LDL-C), and HDL-cholesterol (HDL-C). Serum was separated by centrifuge and stored frozen at -30°C until analysis. Fasting glucose were done within 30 mins after blood collection by colorimetric method at Nam Dinh Endocrinology Hospital. Other analyses were carried out at Vietnam's NIN. Levels of TC, TG and HDL-C were measured by enzymatic colorimetric method. HbA1c was estimated by nephelometry method. Laboratory technologists were blinded to the identity of subjects and intervention status.

Anthropometric measurements

Weight, height, waist and hip circumferences and body fat percentage were measured three times, and the mean was used for analysis. Weight and height were measured while standing, wearing light clothing and without shoes. BMI was calculated as weight (kg) divided by the square of height (m^2). Waist circumference was measured mid-way between the umbilicus and the iliac crest, whereas hip circumference was measured at the widest circumference around the buttocks. Waist-hip ratio (WHR) was calculated as waist circumference (cm) divided by hip circumference (cm). Body fat percentage was measured by the bioelectrical impedance method (HBF-351, Omron Co., Kyoto, Japan).

Nutrition survey

A nutrition survey for 3 non-consecutive days by the 24h recall method was implemented at baseline and final. During interviews, a full-size photo album of common food samples and standard household measures (cups, bowls, etc.) were used to facilitate the survey and increase the accuracy of food description. Energy and nutrient intake were calculated based on the Vietnamese Food Composition Table 2007. Fiber of PGBR was calculated using the data of a previous study on short grain rice (Japonica variety).

Statistical analysis

Qualitative variables were confirmed for normal distribution and compared using Student's *t*-test (paired and unpaired). Numerical data were presented as mean±SD. Values of $p<0.05$ were considered statistically significant for all analysis results. All statistical procedures were performed with SPSS software for Windows version 20.0 (SPSS, Inc., Chicago, IL).

RESULTS

Two participants from WR group and one from PGBR group withdrew from the study citing personal reasons. Data of two subjects were excluded for non-compliance. As a result, data of 55 subjects were presented in this study. Table 1 shows the physical characteristics and blood biochemical parameters of the subjects at baseline. At the outset of the study, except for hip circumference and footstep counts, no statistical differences were identified between two groups in age, weight, height, BMI, body fat percentage, waist circumference, WHR, fasting blood glucose, HbA1c, TG, TC, LDL-C and HDL-C.

Table 2 shows the comparison of physical characteristics and blood biochemical parameters of the PGBR and WR groups at baseline and final. Body fat percentage decreased significantly in both groups at final. Physical activity intensity (represented by footstep counts) of participants within each group remained constant during the time of intervention (p=0.206 in the PGBR and p=0.713 in the WR group). Glucose and HbA1c levels of the PGBR group at final remarkably declined in comparison with that at baseline, whereas in the WR group such changes were not detected.

Table 1. Comparison of physical characteristics and blood biochemical parameters between PGBR group and WR group at baseline.

Variables	PGBR (n=28)	WR (n=27)	p-value
Age (y)	61±9	59±7	0.32
Weight (kg)	60.06±8.96	57.82±10.38	0.395
Height (m)	1.58±0.08	1.57±0.08	0.713
BMI	23.9±2.39	23.2±2.88	0.328
Body fat (%)	30.0±6.3	29.34±6.6	0.698
Waist (cm)	85.8±7.4	84.0±6.5	0.343
Hip (cm)	91.3±4.9	88.6±4.8	0.043
Waist-hip ratio	0.94±0.6	0.95±0.36	0.584
Footstep counts	5339±2667	8251±4132	0.026
Glucose (mmol/L)	9.17±1.80	10.0±1.80	0.089
TC (mmol/L)	5.04±0.77	4.96±0.91	0.74
HDL-C (mmol/L)	1.3±0.135	1.31±0.16	0.643
LDL-C (mmol/L)	2.82±0.50	2.84±0.87	0.937
TG (mmol/L)	2.38±2.00	2.99±2.85	0.364
HbA1c (%)	6.92±0.36	7.03±0.46	0.349

Data are mean±SD. P-values obtained by unpaired t-test. TC: Total cholesterol. HDL-C: High density lipoprotein-cholesterol, LDL-C: low-density lipoprotein-cholesterol, TG: triacylglycerol, HbA1c: hemoglobin A1c.

Table 2. Comparison of physical characteristics and blood biochemical parameters in PGBR group and WR group at baseline and final.

Variables	PGBR group (n=28)			WR group (n=27)		
	Baseline	Final	p-value	Before	Final	p-value
Weight (kg)	60.06±8.96	60.18±8.97	0.531	57.82±10.38	57.80±10.7	0.964
BMI	23.9±2.39	23.9±2.54	0.688	23.2±2.88	23.2±2.94	0.864
Body fat (%)	30.0±6.3	28.5±6.6	<0.001	29.34±6.6	26.98±6.66	<0.001
Waist (cm)	85.8±7.4	86.79±7.0	0.45	84.0±6.5	84.03±6.16	0.935
Hip (cm)	91.3±4.9	90.65±5.7	0.114	88.6±4.8	88.1±5.5	0.357
Waist-hip ratio	0.94±0.06	0.96±0.05	0.007	0.95±0.036	0.95±0.04	0.307
Footstep counts	5339±2667	6064±3279	0.206	8251±4132	7857±3707	0.713
Glucose (mmol/L)	9.17±1.80	7.96±2.3	0.021	10.0±1.80	9.73±2.83	0.639
TC (mmol/L)	5.04±0.77	4.75±0.69	0.05	4.96±0.91	4.74±0.71	0.296
HDL-C (mmol/L)	1.3±0.135	1.22±0.17	0.071	1.31±0.16	1.17±0.16	0.003
LDL-C (mmol/L)	2.82±0.50	2.84±0.51	0.851	2.84±0.87	2.87±0.57	0.798
TG (mmol/L)	2.38±2.00	1.75±0.64	0.083	2.99±2.85	1.87±0.92	0.029
HbA1c (%)	6.92±0.36	6.2±0.77	<0.001	7.03±0.46	7.12±0.84	0.626

Data are mean±SD. P-values obtained by paired t-test. TC: Total cholesterol. HDL-C: High density lipoprotein-cholesterol, LDL-C: low-density lipoprotein-cholesterol, TG: triacylglycerol, HbA1c: hemoglobin A1c.

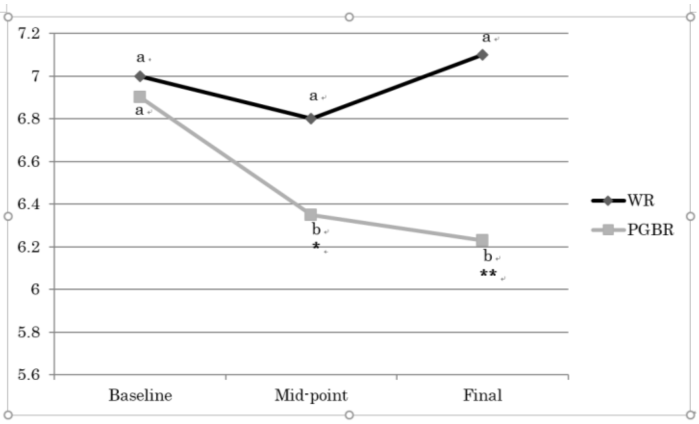

Figure 1. Changes in HbA1c

Different letters denote statistical significance within a group (p<0.05).

**, ** Significant differences between WR and PGBR groups at p<0.05 and p<0.001, respectively.*

Figure 1 shows the changes in HbA1c levels of the two groups during the time of intervention. Within one month and a half after the study implementation, HbA1c mean value of the PGBR group drastically declined from 6.9 to 6.5, which is the cut-off point for DM diagnosis as recommended by WHO. At the middle of the study, HbA1c levels of the PGBR group dropped to 6.4. Average HbA1c value of the PGBR group at the end of the study was 6.2, indicating a significant reduction compared to the baseline (p<0.001). Such decreases were not observed within the WR group (HbA1c 7.0 and 7.1 as initial and final values, respectively). In addition, no meaningful difference in HbA1c levels was detected among both groups at the beginning of the study (p=0.33). Between-group disparity emerged two months after the baseline (p=0.001) and was further emphasized at the final (p<0.001).

Table 3 shows the energy and nutrient intakes of the PGBR and WR groups at baseline and final. The intakes of energy, protein, lipid and carbohydrates between the two groups were similar. Mean fiber intake of the PGBR group at final was 10.9 g/day, significantly higher (p=0.05) than that of the WR group (7.7 g/day), despite the similarity between the two values at baseline.

Table 3. Energy and nutrient intakes of PGBR group and WR group at baseline and final.

Variables	Baseline			Final		
	PGBR (n=28)	WR (n=27)	p-value	PGBR (n=28)	WR (n=27)	p-value
Energy (kcal)	1485±381	1453±360	0.758	1448±329	1462±256	0.86
Carbohydrates (g)	228±63.7	237±65.5	0.63	237±57.4	231±59.4	0.689
Protein (g)	60.4±15.3	61.2±20	0.87	61±15.4	58.2±11.6	0.44
Lipid (g)	35.9±18.6	29.1±11.6	0.11	28.7±9.2	34±11.1	0.56
Dietary fiber (g)	7.9±4.8	7.9±3.2	0.959	10.9±4.6	7.7±3.2	0.05

p-values obtained by unpaired t-test

DISCUSSION

Despite medicine administration, HbA1c levels in the WR group barely changed during the time of the study. On the other hand, HbA1c levels of the PGBR group dropped drastically, and after two months of intervention, it was lower than the cut-off value for DM diagnosis according to WHO (HbA1c≥6.5%). Significant differences in HbA1c levels between two groups were evident at the midpoint of the study and were further expanded at the final. Participants of the PGBR group were administered the same types of medicine as those in the WR group, indicating that a combination of medication treatment and PGBR diet was more effective than the single administration of anti-diabetic agents after a few years. The current data suggest that consuming PGBR in place of WR may be useful in modulating blood glucose in Vietnamese type 2 DM patients.

WR is the principle staple food consumed in Vietnam, where 66% of the energy intake was contributed by rice. As previously reported, the average BMI of newly diagnosed DM patients in Vietnam was approximately 23. High WR intake is considered a major cause of DM at low BMI in Asian populations, since WR has been classified as a high GI food. To produce WR, bran and germ of BR is eliminated through milling and refining processes, which dispossess WR of vital nutrients and phytonutrients, including dietary fiber, minerals, GABA, oryzanols, and fatty acids (11, 22-23). WR therefore is mainly composed of starchy endosperm and is rich in refined carbohydrates, which explains the high GI value. BR and PGBR, on the other hand, retain the dietary fiber-rich rice bran, which makes the most prominent distinction between them and WR. Compared to WR, BR and PGBR have lower GI values, and have been demonstrated to attenuate glycemic response (21-23, 35).

It is noteworthy that in the current study, dietary fiber intakes of the subjects at baseline were around 8 g/day, substantially lower than the recommended intake of 18-20 g/day by Vietnam's Ministry of Health (25). In line with previous papers, the present results revealed a marked difference in dietary fiber intake of the two study groups at final, with mean fiber intake of the PGBR group being significantly higher (10.9 g/day and 7.7 g/day in the PGBR and WR group, respectively). Dietary fiber has been known to be beneficial in regulating blood glucose and lipid concentrations (26-28). In the gastrointestinal tract, fiber passes through unabsorbed and unchanged. Fiber increases bulk of intestinal contents and viscosity of digestive solutions, blunting the diffusion of glucose to the intestinal walls, decelerating the processes of carbohydrate digestion as well as glucose absorption (27). As a consequence, sugar is absorbed into the bloodstream more slowly, and the following increment of the post-prandial blood glucose level is reduced in rapidity. This may be one of the chief physiological mechanisms correlated with GI values of foods, giving an explanation for the difference in GI classification among WR, BR and PGBR. Substitution of PGBR for WR was shown to significantly lower the threat of developing diabetes risk factors, and the credits were given to dietary fiber contents in PGBR bran (21-22, 24). Therefore, a daily addition of 3 g fiber in the diet of the PGBR group may be one of the foremost factors contributing to the HbA1c improvement found in this study.

Fiber may not be the sole factor explaining the results of the present study. GABA, γ-oryzanol and ASG are among various bioactive components of which concentrations were potentiated during the germination process of PGBR. GABA is the main inhibitory neurotransmitter produced by pancreatic β-cells and was demonstrated to induce stimulated insulin secretion (28). In PGBR, GABA concentration is 5-8 times higher than that of WR (21). Recent studies have shown that GABA improved hyperglycemia of diabetic mouse models and promoted β-cell proliferation (28-30). It has been reported that in grafted human islets, GABA activates a Ca^{2+}-dependent signaling pathway through $GABA_A$ receptor and $GABA_B$ receptor, a process in which activation of phosphatidylinositol 3-kinase (PI3K)/AKT signaling is involved. PI3K/AKT is known to be critical for the modulation of β-cell mass and acts in response to Glucagon-like peptide-1 (GLP-1) and glucose in rodents (31), which is in accord with findings by Purwana et al (30) in human islets. It can be presumed from GABA administration outcomes that the improvement in blood glucose concentration may be derived from beneficial impacts of GABA in fortifying human β-cell mass, increasing human insulin circulation, and decreasing glucagon levels. γ-oryzanol is another major bioactive components found in BR as well as PGBR. It is a compound of ferulic acid esters with phytosterols. Oryzanol (Orz) has been reported to ameliorate glucose intolerance and significantly reduced hypothalamic endoplasmic reticulum (ER) stress in rodents. Hypothalamic ER stress has been known as a factor in systemic glucose intolerance by inducing ER stress in the liver and adipose tissue, while an 8-week oral Orz treatment was confirmed to improve glucose metabolism in high fat diet fed mice (32). Preclinical findings have shown multiple effects of oryzanol and ferulic acid, including anti-oxidative (32-33), anti-hypoadiponectinemia and anti-hyperlipidemia (34-35). Furthermore, ASG contents found in PGBR bran was reported by Usuki et al to increase Insulin growth factor-1 (GF-1) generation in pancreatic β-cells of streptocizotocin-induced diabetic rats, which in turn remarkably reduced hyperglycemia (36). ASG was concurrently demonstrated to recover the streptocizotocin-induced decrease in activities of homocysteine-thiolactonase (HTase), an anti-oxidant enzyme whose activation is associated with decreased glycolysis in oxidative-stressed cells.

Until now, preclinical studies have evaluated effects of GABA, oryzanol, ASG and other PGBR components as individual bioactive compounds, at times with much higher doses compared to those available in PGBR. Purwana et al administrated 6-30 mg GABA per 1 mL drinking water on rodents (30), while GABA concentration in PGBR was 3-15 mg/100 g rice (21-22). Nevertheless, PGBR diet administrations have exhibited significant outcomes as reported by several previous papers. This suggests that the improvement in HbA1c found in this study were elicited from the synergy among various bioactive compounds in combination with dietary fiber when consumed as a whole food (PGBR), rather than the impacts of any individual components (37-38). It is likely that the overall synchronous activities of these compounds, or "food energy" (39), were what optimized the comprehensive effects, as evidenced by the noteworthy outcomes of PGBR diet.

As opposed to fasting blood glucose concentration level which is afflicted by daily fluctuations, HbA1c is a more reliable measure for clinical assessment of glycemic control in DM patients (39). HbA1c is formed by non-enzymatic attachment of glucose to the N-terminal valine of the hemoglobin β-chain (40). The concentration of HbA_{1c} depends on both the blood glucose concentration and the life span of the red blood cells (RBCs). As human RBCs live in blood circulation for roughly 100-120 days, HbA_{1c} level reflects the glucose concentration accumulated over a course of 8–12 weeks (41). Accordingly, this study was designed to last 4 months to accurately elucidate the effects of PGBR on HbA1c levels of the subjects.

Preliminary results in physical activity intensity (represented by footstep counts) of both groups exhibited particular difference (p=0.026). However, over the 4-month intervention, both groups showed no sign of any within-group changes in physical activity intensity (p=0.206 and p=0.713 in PGBR group and WR group, respectively). Despite the fact that marked declines in body fat percentage were observed, no significant difference was found in body weight among both groups, in contrast with the results of a previous study (24). As type 2 DM patients, all subjects strictly follow their individualized diet, as reflected in the similar energy and nutrient intake at baseline and final in both groups. It is widely known that energy balance is what control body weight. Therefore, the stability in body weight observed in our data can be explained by the well balanced energy intake and constant physical activity intensity of study participants. A study with similar design in younger, non-diabetic subjects has been planned to corroborate the previous body weight results.

CONCLUSION

The present study suggests that substitution of WR with PGBR can improve HbA1c levels of Vietnamese type 2 DM patients who have been under long-term oral diabetes treatment. In Vietnam where rice contributes to 67% of the daily caloric intake, the escalation of T2DM cases could be regulated owing in large part to the widespread use of PGBR.

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