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Research Article

HYPOGLYCEMIC EFFECT OF HIGH-RESISTANT STARCH ANALOG RICE THROUGH GLP-1 AND INSULIN OR HIGH-RESISTANT STARCH ANALOG RICE ATTENUATES BLOOD GLUCOSE LEVEL THROUGH ENHANCEMENT OF GLP-1 AND INSULIN

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ABSTRACT

Objective: This study was to investigate the effect of analog rice (AR) on glucagon-like peptide-1 (GLP-1) and insulin serum levels, glucose transporter-2 (GLUT-2) expression, and fasting blood glucose (FBG) level in diabetic rats.

Methods: Fifty male Wistar rats divided into the control group (n=10) and the experimental group. High-fat diet and streptozotocin were administered in experimental groups, which then divided into four equal groups (n=10, each) (negative control group, rice group, AR1 and AR2 group, given standard pellet, rice pellet, AR1 and AR2 pellet, respectively, for 6 weeks). GLP-1 and insulin serum levels were measured by enzyme-linked immunosorbent assay. The expression of GLUT-2 and the number of pancreatic β-cells observed using an immunohistochemistry method.

Results: FBG levels in the AR1 and AR2 groups decreased, while the rice group remained. GLP-1 serum levels of the negative control and rice groups were not significantly different from the control group, while the AR1 and AR2 groups higher than the control group ($p \leq 0.05$). All the treatment groups had insulin serum levels significantly lower than control group ($p \leq 0.05$), except the AR1 group. The expression of GLUT-2 and the number of pancreatic β-cells in the treatment groups were less than the control group, but between treatment groups were not significantly different.

Conclusion: AR significantly effective in reducing FBG level in diabetic rats through stimulation of increased GLP-1 and insulin serum levels serum levels but AR did not affect on the expression of GLUT-2.

Keywords: Analog rice, Resistant starch, Glucagon-like peptide-1, Insulin, Glucose transporter-2, β-cell.

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INTRODUCTION

Diabetes mellitus (DM) prevalence worldwide increased by 11% within 4 years. In 2013, the number of diabetic patients was 381.8 million [1] and increased to 425 million in 2017 [2,3]. It is estimated that DM patients in the world will reach 591.9 million in 2035 [1,2]. DM is a troubling disease because it causes many complications, both acute and chronic. Such complications include stroke, heart failure, kidney failure, sexual dysfunction, cataracts, and gangrene [2,4].

DM management needs to integrate the drug therapy [5], diet [6,7], exercise [7,8], and possible complementary treatments [9]. The successful management of DM is influenced by lifestyle [7,9], includes eating habits [4,6,7]. Most of the world's population has eating habits using easily absorbed foods, rich in carbohydrates, low in fiber, and resistant starch (RS), such as rice. DM patients who consume rice as a staple food can result in suboptimal control of blood glucose [10]. This can contribute to therapeutic failure of DM; therefore, we need to find a substitute staple food.

Analog rice (AR) can be considered as an alternative diet management for diabetic patients. AR is artificial rice which has adjustable composition according to the needs. It can contain high RS and high-fiber ingredients. Former studies reported that high-fiber diet could improve blood glucose control and attenuate hyperinsulinemia in DM type 2 patients [6,11]. Therefore, this study was to analyze the mechanism of blood glucose improvement after AR consumption in diabetic rat model.

METHODS

Ethical clearance was obtained from the Animal Care and Use Committee Veterinary Faculty, Airlangga University, No. 667-KE/2017.

Making rice pellets, AR, and AR pellets

Rice pellet was made by substituting 60% of carbohydrate content of standard pellet with rice (IR 64). AR was produced using hot extruder technology with twin screws [12]. The compositions are found in Table 1. There are two types of AR, each named AR 1 and AR 2. AR pellets were made by substituting 60% of carbohydrate content from standard pellets with each type of AR. All the pellets have the same calories (iso calories).

Rat preparation

A total of 55 rats Wistar strain, 3 months old, body weight 160–200 g, were randomly divided into control group (n=10) and experimental group (n=45). The control group was fed with standard feed formula for 3 weeks, whereas the experimental group was fed with high-fat diet (HFD) containing 23% fat (lard fat) for 3 weeks and injected with streptozotocin (STZ) (BioWORLD) 35 mg/kg intraperitoneal at the end of the 2nd week (14th day). The STZ was dissolved in citrate buffer (0.05 M, pH 4.5) [13,14]. At the end of the 3th week of HFD administration (21th) or After 7 day of injection of STZ. FBG levels of all the rats were measured through the tip of the rats tail [13,14], using glucometer (Easy Touch, Taiwan). The experimental group which had fasting blood glucose (FBG) levels between 300–450 mg/dl was randomly divided into four equal groups, each of 10 rats per group, namely: (1) Negative

control group: Fed with standard pellets; (2) rice group: Fed with rice pellets; (3) AR1 group: Fed with AR1 pellets; and (4) AR2 group: Fed with AR2 pellets. Each pellet was given *ad libitum* for 6 weeks. At the end of the 6th week, after being pellets provisioning, the rats were fasted for 8 h then measured blood glucose level using glucometer. Moreover, the rats were terminate; then, the blood and pancreas were taken for the measurement of research parameters.

Research parameters measurement

FBG levels were measured from 8-h fasting rats using glucometer. Glucagon-like peptide-1 (GLP-1) serum levels were measured by the enzyme-linked immunosorbent assay (ELISA) method using rat GLP-1 ELISA assay kit (produced by Novateinbio). Data were expressed as ng/ml. Insulin serum levels were measured by the ELISA method, using rat insulin ELISA assay kit (produced by Novateinbio). Data were expressed as μIU/ml. Immunohistochemistry analysis of the expression of glucose transporter-2 (GLUT-2) and the number of pancreatic β-cells used single-stain monoclonal antibody. Expression of GLUT-2 was calculated from cell that contains GLUT-2 bonds with GLUT-2 monoclonal antibodies. Pancreatic β-cells with purple color were scored for the presence of GLUT-2 with brown color. It was quantitatively measured by counting on 10 selected high-power fields (×400) using light microscope.

RESULTS

Rice (original rice) does not contain RS. Meanwhile, AR1 and AR2, each has 16.83% and 11.46% RS (Table 2). AR has 4 times higher in fiber content than original rice. Among them, AR1 has the highest fiber which is 1.77%.

FBG level

There was no difference in pre-induction the FBG level between groups. Post-induction FBG level of the control group did not change, whereas post-induction FBG level of the experimental groups has increased, but there was no significant difference on FBG levels between the experimental groups. After 6 weeks of diet therapy, the FBG of control group was 94.95±0.51 mg/dl. The FBG level in the control negative and rice groups did not differ significantly, while the AR1 and AR2 groups decreased significantly.

The GLP-1 and insulin serum levels

The mean of GLP-1 serum level of control group was 46.09±4.3 ng/ml. The mean of GLP-1 serum levels of negative control and rice groups did not differ significantly with control group (p≤0.05), while AR1 and AR2 groups increased significantly. The GLP-1 serum level AR1 group was higher than AR2 group but was not significantly. The mean insulin serum level in the control group was 136.21±17.4 μIU/ml. All experimental groups had significantly lower serum insulin levels than the control group (p≤0.05), except AR1 group. AR1 and AR2 groups had significantly higher serum insulin levels than rice group.

The expression of GLUT-2 and the number of pancreatic β-cells

Observations on β-cells in the islets of Langerhans showed that experimental groups had pancreatic β-cells damaged so that the number of the cells less than the control group significantly. The diameter or the area islets of Langerhans of experimental groups was shorter or narrower than control group. Expression of GLUT-2 of pancreatic β-cells was not different significantly between experimental groups.

Table 1: The composition of analog rice

Ingredient	AR1	AR2
Modified cassava flour	16.2	32.4
Rice flour	21.6	5.4
Cornstarch	16.2	16.2
Soy protein	3.9	3.9
Palm oil	1.4	2.1
Sodium alginate	0.7	0.0
Total	60.0	60.0

AR1: Analog rice 1, AR2: Analog rice 2, MOCAF produced by PT Bangkit Cassava Mandiri, Indonesia. Produced from fermented cassava and then made into flour [12]. All measured in g. MOCAF: Modified cassava flour

Table 2: Calorie, fiber, and RS content in 100 g analog rice

Description	Calorie (cal)	Fiber (g)	RS (g)
Rice	398.4	0.41	0,00
AR1	382.7	1.77	16.83
AR2	379.8	0.86	11.46

RS: Resistant starch, AR1: Analog rice 1, AR2: Analog rice 2. Calorie was measured in calorie. Fiber and RS were measured in g

DISCUSSION

The effects of AR on GLP-1 serum level in diabetic rats

The GLP-1 serum level on negative control group and rice group was not different from the control group. This indicates that the administration of HFD and STZ did not affect in significant changes on GLP-1 serum level and the administration of rice for 6 weeks has not been shown to significantly increase GLP-1 serum levels. These results indicated that GLP-1 serum level in diabetes was normal and administration of rice did not increase GLP-1 serum level (Table 3).

The administration of AR for 6 weeks has been shown to increase GLP-1 serum levels significantly. This effect occurs because AR has a high RS and fiber. Correlation test showed a significant relationship between GLP-1 serum level with RS (0.736) and fiber (0.733). RS and fiber inhibit the digestion and absorption of food in the intestine and accelerating the onset of satiety [11,15,16]. This effect leads to the stimulation of L cells in the intestine to secrete GLP-1 [17].

The RS [18,19] and fiber [10] cannot be digested; then, it will be fermented by the microbiota in the intestine [18-20] and generated short-chain fatty acid (SCFA) [17,20]. SCFA can stimulate intestinal L cells which result in an increase on GLP-1 secretion of the cells [17,18]. The results of another study showed that administration of an acute a fiber-rich diet had no effect on plasma levels of GLP-1 [21]. In this study, diabetic rats were given AR which rich in fiber for 6 weeks. The results showed different effects, fiber has a strong effect on increasing GLP-1 serum levels. This fact suggests that the provision of fiber has increasing effect on GLP-1 level if given repeatedly. The provision of fiber takes a long time to increase in GLP-1 serum level. AR1 is stronger than AR2 to increase GLP-1 serum levels due to higher levels of RS and fiber.

The effects of AR on the expression of GLUT-2 and the number of pancreatic β-cells

The results obtained in this study indicate that an increase in GLP-1 serum level in the AR1 and AR2 group was not followed by an increase in expression of GLUT-2 and number (total) of pancreatic β-cells (Table 4).

Table 4 shows that the amount of pancreatic beta-cells which expressing GLUT-2 in the experimental group did not differ significantly from the

Table 3: GLP-1 and insulin serum levels

Group	GLP-1	Insulin
Control	46.09±04.3	136.21±17.4
Negative control	44.89±11.2	90.12±20.8
Rice	38.65±14.4	82.65±16.6
AR1	84.29±20.9	128.17±16.1
AR2	65.07±10.6	112.53±23.7

n=10, values are given as mean±SD, GLP-1: Glucagon-like peptide-1 was measured in ng/ml, insulin was measured in μIU/ml, AR1: Analog rice 1, AR2: Analog rice 2. SD: Standard deviation

control group. Since GLP-1 serum levels in the AR1 and AR2 groups increased, but GLUT-2 expression and the number of β-cells of pancreas were not different (not change) compared to the negative control group, we suspected that GLP-1 had no stimulating effect on GLUT-2 expression and pancreatic β-cell regeneration. The results of statistics analysis showed no association between GLP-1 with GLUT-2 expression and amount of β-cell of pancreas ($p>0.05$). The results of this study differ from the previous studies which stated that GLP-1 might stimulate GLUT-2 expression, thereby increasing the sensitivity of pancreatic β-cells [21].

Immunohistochemistry analysis of the pancreas (Fig. 1) revealed that the diameter of the islets of Langerhans in all experimental groups was shorter than the control group. The number of pancreatic β-cells in the islets also decreased significantly (Table 4). This change occurs due to the administration of STZ which results in damage to β-cells of pancreas. After giving the AR for 6 weeks, there was no increasing diameter from the islets of Langerhans or the number of pancreatic β-cells. Therefore, it was taken together from the data a conclusion that giving AR does not provide stimulation for pancreatic β-cell regeneration.

The effects of AR on insulin serum levels

The number of pancreatic β-cells which decreased in the experimental group resulted in decreased insulin secretion so that insulin serum levels in the experimental groups were lower than the control group. In Table 3, it can be seen that insulin serum level in the negative control group is lower than the control group. Table 3 shows that giving rice diet for 6 weeks cannot increase insulin serum levels, otherwise giving AR for 6 weeks can increase insulin serum level in diabetic rats. That is because AR has higher levels of RS and fiber than rice, so AR can increase GLP-1 higher than rice. Furthermore, GLP-1 stimulates insulin secretion [15].

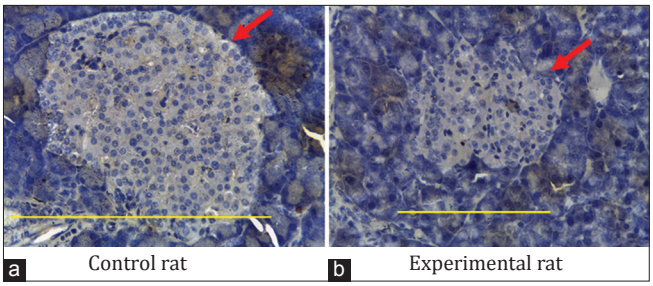

Fig. 1: Histology of the control rat pancreas (a), histology of the induced (diabetes mellitus) rat pancreas (b). The red arrows indicate the islets of Langerhans, the yellow line indicates the diameter the islets, IHC ×400

There are several possible mechanisms that correlate the increase in serum GLP-1 with insulin serum level, namely: (1) pancreatic β-cell protective or prevention of apoptosis [22] and proliferation pancreatic β-cells [15] so that the number of the cells increases; (2) stimulating GLUT-2 expression [23,24].

The facts obtained from this research showed no significant difference in the expression of GLUT-2 and the number of pancreatic β-cells between groups although there were differences in GLP-1 serum levels. This proves that the stimulation effect on insulin secretion by GLP-1 was not through increased expression of GLUT-2 or an increase in the number of pancreatic β-cell. Hence, the effect of stimulation on insulin secretion by GLP-1 was likely through an increase in the number of receptors [15,23] or through other mechanisms such as stimulation on hexokinase activity [23].

The assumption mechanism for increasing insulin secretion through increasing the number of these receptors according to with the alleged effects of GLP-1 on insulin secretion occurs through activation adenylyl cyclase. This activation resulted in increased cyclic adenosine monophosphate and protein kinase A activity. This condition results in increased levels of intracellular calcium resulting in an increase in exocytosis (secretion) of insulin [25]. Hence, the more receptors the more insulin secretions. The effect of AR1 in stimulating insulin secretion was stronger than AR2. Administration of AR1 can restore insulin serum levels which are almost the same as control group, while AR2 increases insulin serum levels but has not been able to return to normal levels.

The effects of AR on FBG level in diabetic rats

After getting diet therapy for 6 weeks, FBG level in the negative control and rice group has not differ significantly, whereas the AR1 and AR2 groups have decreased significantly (Table 5). The decrease in FBG in the AR1 and AR2 groups could be due to the effect of RS and fiber on AR. RS [19] and fiber [11] have the effect of inhibiting the digestion process because it can inhibit the activity of digestive enzymes, resulting in more controlled blood glucose levels. This statement is consistent with other studies that prove fiber plays a role in controlling blood glucose levels. These effects associated with barriers to digestion and absorption of carbohydrates [26].

RS [20] and fiber [11] in the large intestine will be fermented by microbiota and produce SCFA [27,28]. Furthermore, SCFA stimulates GLP-1 secretion, hereafter, GLP-1 stimulates insulin secretion. Increased insulin secretion results in a decrease in blood glucose levels.

SCFA also has the effect of inhibiting activity of hormone-sensitive lipase in the blood [28] so that there was a decrease in lipolysis; furthermore,

Table 4: The expression of GLUT-2 and the number of pancreatic β-cells

Group	β-cells with expression of GLUT-2	β-cells without expression of GLUT-2	Total β-cell
Control	11.65±5.1	20.15±7.9	31.80±7.3
Negative control	8.45±2.7	8.08±3.0	16.53±5.6
Rice	8.16±2.3	10.76±5.1	18.92±6.8
AR1	7.95±1.8	9.50±2.5	17.45±3.4
AR2	7.55±6.0	10.44±3.7	17.99±4.3

n=10, values are given as mean±SD, GLUT-2: Glucose transporter-2, AR1: Analog rice 1, AR2: Analog rice 2. SD: Standard deviation

Table 5: Fasting blood glucose levels pre- and post-induction and post-therapy

Group	FBG		
	Pre-induction	Post-induction	Post-therapy
Control	93.70±6.3	96.25±04.5	94.95±05.1
Negative control	93.40±6.3	367.75±23.6	303.25±16.8
Rice	94.30±7.6	366.25±26.4	378.00±13.2
AR1	93.50±6.4	366.70±29.8	125.05±12.1
AR2	93.95±6.6	368.50±28.3	152.00±25.4

n=10, values are given as mean±SD, FBG: Fasting blood glucose is measured in mg/dl, AR1: Analog rice 1, AR2: Analog rice 2. SD: Standard deviation

the free fatty acid (FFA) will decrease. Decreasing levels of FFA in the blood will increase insulin sensitivity [28] and reduce resistance to hexokinase enzyme activity; thereby, glycolysis and glycogenesis will increase so that the blood glucose levels decrease [20,27,29]. Because AR1 and AR1 contain high RS and fiber, it will be absorbed more slowly. Foods that are slower in absorption will have a lower glycemic index so that AR1 and AR have the opportunity to be developed into a staple food for DM patients.

CONCLUSION

Based on these results, we concluded that AR significantly effective in reducing blood glucose level in diabetic rats through stimulation of increased GLP-1 and insulin serum levels but does not affect the expression of GLUT-2 and the number of pancreatic β-cell. The highlight of this study was that AR1 showed a strong effect in reducing blood glucose levels so that it has the potential to be developed as a staple food substitute for DM patients.

AUTHORS' CONTRIBUTIONS

The topic of the research came from the first author. All the authors have the same contribution in carried out the research, determine the research method, collected and analyzed the data, and formatted these manuscripts.

CONFLICTS OF INTEREST

The authors declare that there are no potential conflicts of interest regarding the publication of this paper.

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