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Research Article
Fiber Increases Endogenous Insulin and Reduces Insulin Resistance in Diabetes

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Abstract
Background and Objective: Dietary fibers have been identified to have beneficial effects in improving insulin secretion and insulin resistance. This study aimed to evaluate the effects of fiber-rich snacks on insulin secretion and insulin resistance in patients with type 2 diabetes mellitus (T2DM). **Materials and Methods:** Twenty patients with T2DM, ages 40-60 years were recruited from the Polyclinic of Endocrine, General Hospital Dr. Sardjito, Yogyakarta, Indonesia. The subjects received daily 32 g snacks made from a mixture of *Dioscorea esculenta*, arrowroot, cassava and pumpkin, for 4 weeks. Fasting plasma glucose, insulin and C-peptide levels were measured before and after intervention. Paired t-tests were used to evaluate the results. **Results:** Intervention of fiber-rich snacks for 4 weeks for T2DM patients significantly ($p = 0.01$) reduced fasting plasma glucose from 9.3 ± 2.7 to 8.3 ± 2.5 mmol L^{-1} and homeostatic model assessment of insulin resistance ($p = 0.04$) from 4.1 ± 1.3 to 3.6 ± 1.9 and significantly ($p<0.001$) increased C-peptide levels from 0.417 ± 0.004 to 0.512 ± 0.008 ng mL^{-1}. **Conclusion:** In this study, fiber-rich snacks provide significant benefits to increase endogenous insulin secretion and reduce insulin resistance in patients with T2DM.

Key words: Body mass index, dietary fiber, HOMA-IR, insulin resistance index, lipid profile, snack supplement, T2DM

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Insulin resistance has been recognized as the most powerful predictor for the development of type 2 diabetes mellitus (T2DM) and is considered an important therapeutic target for patients with hyperglycemia. Insulin resistance is usually associated with abnormal insulin secretion[1]. In pancreatic beta cells, proinsulin is cleaved by prohormone convertase, carboxypeptidases and endopeptidase releasing insulin and C-peptide from proinsulin in equimolar concentrations[2]. C-peptide is considered as the best measure of endogenous insulin secretion in diabetic patients[3] and was reported to have negatively correlations with insulin sensitivity, so it can be used to monitor insulin resistance[4]. Low levels of C-peptide were reported to be associated with diabetic complications including nephropathy and peripheral neuropathy[2] and the fasting serum C-peptide levels (>1.6 ng mL^{-1}) can predict insulin resistance in T2DM[5].

Insulin resistance is a glucose homeostasis disorder directly influenced by refined sugar and carbohydrate intake, including dietary fiber and dietary carbohydrate to fiber ratio is strongly associated with insulin resistance[6]. Some studies reported that dietary fiber can improve insulin resistance. Chen *et al.*[7] reported that fasting blood glucose and insulin resistance index in T2DM patients improved significantly after giving dietary fiber for one month. According to Wheeler *et al.*[8], moderate amounts of daily fiber supplementation (4-19 g) improved glycemic or cardiovascular risk. The glucose response to dietary fiber is followed by a C-peptide response[9]. The amount and quality of dietary fiber influence the glucose and C-peptide responses. Resistant starch, a type of dietary oligo-fructose, increase insulin sensitivity and hepatic insulin clearance, also decrease postprandial insulin responses. Overweight individuals who received 40 g of type 2 resistant starch for four weeks had significantly higher insulin and C-peptide concentrations than those who received a placebo[10]. Therefore, this study evaluated the beneficial effects of high-fiber snacks made from a mixture of *Dioscorea esculenta*, arrowroot, cassava and pumpkin on endogenous insulin secretion and insulin resistance in T2DM patients.

MATERIALS AND METHODS

Subjects: The subjects in this study were voluntary T2DM patients, with age range of 40-60 years, who were recruited from the Polyclinic of Internal Medicine (Endocrine), Central Hospital Dr. Sardjito, Yogyakarta, Indonesia. The inclusion criteria for subjects were: previously diagnosed with T2DM for at least 1 year, fasting blood glucose (FBG) >126 mg dL^{-1} and using administration of oral antidiabetic agents or insulin. Exclusion criteria were: smoker, pregnancy or lactation and blood pressure >140/90 mm Hg.

This study was conducted according to the guidelines established in the Declaration of Helsinki and was approved by the Health and Medical Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia. Written informed consent forms were obtained from all patients. Based on the criteria, 20 patients were included in this study.

Anthropometric measurements: The anthropometric measurements were done twice, before and after high-fiber snacks administration. Height was measured using a microtoise. Karada scan (Omron) was used to measure body weight, body mass index (BMI) and visceral fat.

Intervention: The subjects received detailed written and oral instructions from an experienced dietician about their diet, including the precise amounts to be eaten and the quality of the food products to be consumed. They were proposed to consume daily food with an average energy 1500 kcal and the diet was monitored by means of 3-day food records. The subjects received daily a 32 g snack made from a mixture of *Dioscorea esculenta*, arrowroot, cassava and pumpkin that contains 150 kcal and given for 4 weeks. Contents of 100 g snacks contain water soluble fiber (4.81 g) and insoluble fiber (14.91 g) and provide approximately 451.71 kcal. Monitoring of interventions was done by telephone and the remaining snacks were collected every week to find out the exact amount of snacks that were actually consumed.

Blood sampling / Laboratory methods: Before and after high-fiber snacks administration, the blood samples were collected via median cubital vein and enter into Ethylenediaminetetraacetic acid (EDTA-tube). To obtain the plasma, the EDTA-blood samples were centrifuged at 3000 g for 15 min at room temperature. The EDTA-plasma was used for determination of the glucose levels using the GOD-PAP method (DiaSys, Germany), whereas insulin and C-peptide levels were measured using the ELISA method (DRG, Germany). The homeostatic model assessment of insulin resistance (HOMA-IR) value was calculated as follows: fasting insulin (μIU mL^{-1}) x fasting glucose (mmol mL^{-1})/22.5[11].

Statistical analysis: Paired t-tests were used to evaluate biochemistry and anthropometry parameters before and after administration of snacks. Differences were considered statistically significant at $p<0.05$.

RESULTS

A total of 20 diabetic patients, 9 men and 11 women, mean age 51.9±4.96 years old, were involved in this study. Anthropometric characteristics of the patients before and after the 4-week intervention are presented in Table 1. The reductions of BMI after intervention of fiber-rich snack for 4 weeks were statistically significant ($p = 0.04$) but decreasing of body weight and visceral fat were not significantly different ($p = 0.12$ and $p = 0.64$), respectively.

After fiber-rich snack interventions for 4 weeks, FPG and HOMA-IR levels were significantly lower and C-peptide levels increased significantly but insulin levels did not change. Interventions of fiber-rich snack for 4 weeks also improved the subject's lipid profile. Triglyceride, total cholesterol and LDL levels decreased significantly ($p<0.05$), however, HDL levels also decreased although not significantly ($p> 0.05$) (Table 2).

DISCUSSION

The results showed that administration of daily 32g snack made from a mixture of *Dioscorea esculenta*, arrowroot, cassava and pumpkin can reduce BMI ($p<0.05$) (Table 1). Before intervention, the BMI of the subjects was in the range of 24.09-34.79, indicating some of them were obese which is one of the risk factors for T2DM. The BMI reducing effects of the snacks may be caused by the fiber contents in the snacks, which include soluble fiber (4.81%) and insoluble fiber (14.91%). This fiber content especially from the *Dioscorea esculenta* is in the form of inulin (21.33%) and the arrowroot that contains insoluble fiber (8.7% or 2.78 g) and soluble fiber (5.0% or 1.6 g)[12]. According to Li and Komarek[13], a food containing 2.5-4.9 g of fiber is good source of fiber and 5 g or more fiber per serving is high fiber. Dietary fiber, especially soluble fiber, can delay gastric emptying due mainly to its effects of increasing viscosity of gut content. Lattimer and Haub[14] and Müller *et al.*[15] reported that soluble fibers increase the viscosity of food that induces feeling of fullness, delays gastric emptying and/or physically inhibits absorption of nutrients in the small intestine. According to Li and Uppal[16] soluble dietary fiber promotes satiety via the release of numerous gastric hormones include gastric inhibitory peptide (GIP), Glucagon like peptide 1 (GLP-1), cholecystokinin and peptide YY. The hormones give negatively feedback to the hypothalamic regulation of food intake and feeding behavior. In addition, insoluble fiber can reduce appetite and food intake through the fermentation products of colonic bacteria that are short chain fatty acids (SCFAs)[14]. According to Byrne *et al.*[17] SCFAs affect energy homeostasis and appetite regulation through parallel activation of number of metabolic processes. Ma and Mu[18] reported that giving dietary fiber from deoiled cumin (500 mg kg^{-1} body weight) for 4 weeks improved regulation of blood glucose and insulin, increased levels of SCFAs in colon and decreased fatty degeneration of liver in diabetic rats. The main SCFAs of bacterial fermentation are acetate, propionate and butyrate. The SCFAs activate receptors free fatty acid receptor 2 and 3 (FFA2 and FFA3). In mice, affinity of FFA2 and FFA3 for acetate and butyrate are equal but FFA3 has higher affinity for propionate than FFA2.

Table 1: Anthropometric parameters of subjects before and after intervention of the fiber-rich snacks

Anthropometric parameters	Before	After	Mean difference	Paired t test (p)
Weight (kg)	70.9±10.1	70.4±10.0	0.5	0.12
Visceral fat (%)	11.6±2.2	11.3±2.6	0.4	0.64
BMI ($kg\ m^{-1\ 2}$)*	27.2 (24.1-34.8)	26.8 (24.4-33.7)	0.3	0.04

Values are presented as Mean±standard deviation (SD). n = 20. $p<0.05$ according to paired t test. BMI: Body mass index. *BMI was presented as median (min-max), $p<0.05$ according to Wilcoxon test

Table 2: Biochemical parameters of subjects before and after intervention of the fiber-rich snack

Biochemical parameters	Before	After	Mean difference	Paired t test (p)
FPG (mmol L^{-1})	9.300±2.7	8.300±2.5	-0.900	0.010
HOMA-IR	4.100±1.3	3.600±1.9	-0.400	0.040
C-peptide (ng mL^{-1})	0.417±0.004	0.512±0.008	0.095	<0.001
Insulin (μIu mL^{-1})	9.700±1.4	9.800±3.5	0.100	0.940
Triglyceride (mg dL^{-1})	153.900±65.9	116.300±53.4	-37.700	0.010
Total cholesterol (mg dL^{-1})	200.000±38.6	171.400±33.9	-28.600	0.001
LDL (mg dL^{-1})	135.000±36.9	100.200±24.6	-34.800	<0.001
HDL (mg dL^{-1})	88.000±16.8	78.700±23.0	-9.300	0.090

Values are presented as Mean±standard deviation (SD). n = 20. $p<0.05$ according to paired t test. FPG: Fasting plasma glucose. HOMA-IR: Homeostatic model assessment of insulin resistance. LDL: Low density lipoprotein, HDL: High density lipoprotein

Soluble fiber can form viscous gels that are not digested during transit in the small intestine and are easily fermented by the bacteria in the large intestine[14]. The increased gastrointestinal viscosity can delay gastric emptying and provide longer satiety, thus reducing appetite and the rate of glucose absorption and finally lowering the blood glucose levels. In this study, the FPG and HOMA-IR were significantly decreased (p = 0.01) (Table 2). These results correspond to another research that reported HOMA-IR index was reduced from 1.19-0.88 after the intervention of 8 g resistant starch from unripe banana flour[19], which is one of the dietary fiber fractions[14]. According to Bindels *et al.*[20], dietary resistant starch has a number of metabolic benefits including improvement of insulin sensitivity. According to Li and Uppal[16], insulin sensitivity modulation is not well understood; however, some viscous fibers in meals, such as guar gum can increase its viscosity and delay gastric emptying and intestinal digestion. These have moderate and prolong effect on postprandial glucose release into the circulation, thereby lowering the insulin response. In addition, in hepatocytes, SCFAs increases glucose oxidation, decreases the release of free fatty acid and promotes insulin sensitivity. Another mechanism of dietary fiber increases insulin sensitivity through inducing synthesis of glucagon like peptide 1 (GLP-1). GLP-1 can delay gastric emptying, increase insulin-dependent glucose uptake, inhibit glucagon secretion, stimulate insulin secretion and reduce hepatic glucose production. These processes can collectively reduce the need for insulin[16].

In this study, subjects' C-peptide levels increased significantly, although insulin levels remained relatively unchanged, after giving snacks every day for 4 weeks (Table. 2). According to Khan *et al.*[21], C-peptide roughly indicates the extent of insulin production and release and it can be used to assess pancreatic beta cell function and endogenous insulin production because it has half-life (20-30 min) longer than half-life of insulin (3-5 min)[22]. C-peptide is the 31 amino-acid residues formed during cleavage of insulin from proinsulin, is co-secreted from pancreatic beta cells in equimolar amounts with insulin and considered an inactive by-product of insulin biosynthesis[23]. This result showed that the fiber in this snack can increase endogenous insulin secretion which was indicated by the increases of C-peptide levels, thus improving insulin sensitivity and as a result reducing the levels of FPG.

In this study, the interventions of fiber-rich snack also improved the subject's lipid profile. High levels of total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), triglyceride levels (TG) and low high-density lipoprotein (HDL-C) cholesterol levels are commonly found in diabetic patients. In this study, triglyceride and LDL levels were higher than normal values, TC levels were at the upper limit of normal values but HDL levels were normal (Table 2). The normal values of lipid profile are TG <150 mg dL^{-1}, LDL <130 mg dL^{-1}), TC 130-200 mg dL^{-1} and HDL 40 mg dL^{-1} [24]. Rai *et al.*[25] reported that both T2DM without complications and T2DM with nephropathy had higher TC, TG, LDL-c levels compared to controls. They suggest that early detection of dyslipidemia and appropriate therapeutic interventions can prevent cardiovascular or kidney complications. Therefore, fiber-rich snacks made from a mixture of *Dioscorea esculenta*, arrowroot, cassava and pumpkin can provide potential therapeutic nutrients to prevent complications in diabetic patients.

CONCLUSION

Fiber-rich snacks increased endogenous insulin and reduced insulin resistance in patients with T2DM. Treating physicians are recommended to encourage patients with T2DM to supplement their diet with fiber-rich foods, including tuber sourced snacks. Future research can apply a case/control design with a larger study population to elucidate the importance of fiber in recommended diets for patients with T2DM.

SIGNIFICANCE STATEMENT

This study revealed dietary fiber can increase endogenous insulin and reduce insulin resistance in T2DM patients. Beneficial effects of fiber supplementation also included significantly decreased BMI and improved lipid profiles. We used fiber from *Dioscorea esculenta*, arrowroot, cassava and pumpkin to create snacks that are both delicious and healthy. We hope the results of this study will encourage further research into the benefits of fiber in nutritious diets which are palatable and made from local foods. Findings of the current study contribute to a growing body of research demonstrating the positive effects of specialized diets for type 2 diabetes mellitus patients which are rich in fiber and can help to maintain healthy levels of insulin.

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