*http://rjdnmd.org*
Rom J Diabetes Nutr Metab Dis. **25**(3):271-276
doi: 10.2478/rjdnmd-2018-0031

# EFFECT OF FIBER-RICH SNACKS ON C-REACTIVE PROTEIN AND ATHEROGENIC INDEX IN TYPE 2 DIABETES PATIENTS

***Sunarti*** [1,✉], ***Sri Lestari Sulistyo Rini*** [2], ***Hemi Sinorita*** [3], ***Dini Ariani*** [4]

[1] Department of Biochemistry, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia
[2] Department of Physiology, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia
[3] Department of Internal Medicine, Dr. Sardjito General Hospital, Yogyakarta, Indonesia
[4] Balai Penelitian Teknologi Bahan Alam, Lembaga Ilmu Pengetahuan Indonesia, Gading Playen, Gunungkidul, Yogyakarta, Indonesia

*received*: June 07, 2018 *accepted*: August 28, 2018
*available online*: September 23, 2018

## Abstract

***Background and aims:*** *High levels of non-HDL and atherogenic cholesterol can induce inflammation, and as risk factor for cardiovascular diseases. This study was to evaluate the effects of fiber-rich snacks on non-HDL cholesterol, atherogenic index, and C-reactive protein (CRP) levels in type 2 diabetes patients (T2DM).* ***Material and Methods:*** *Twenty T2DM patients, were recruited from the Policlinic of Endocrine, Dr. Sardjito General Hospital, Yogyakarta, Indonesia. The subjects received daily 32g fiber-rich snacks made of Dioscorea esculenta, arrowroot, cassava and pumpkin for 4 weeks. Fasting non-HDL cholesterol, atherogenic index, CRP and HbA1c levels were measured before and after intervention. Paired t-test was used to evaluate the results.* ***Results:*** *The fiber-rich snack intervention in T2DM patients significantly reduced levels of non-HDL cholesterol and CRP levels ($p<0.05$), but the decreased the atherogenic index was not significant ($p>0.05$). The intervention also significantly reduced the CRP levels ($p<0.05$) but did not affect HbA1c levels. Body weight, body mass index (BMI), waist circumference decreased significantly after consuming the snacks ($p<0.05$).* ***Conclusions:*** *This study showed fiber-rich snack has a positive effect in improving non-HDL cholesterol, atherogenic index and CRP levels but does not affect HbA1c levels in T2DM patients.*

**key words**: *Dietary fiber, non-HDL cholesterol, atherogenic index, C-reactive protein, HbA1c*

## Background and aims

Diabetes mellitus is considered as traditional risk factors for cardiovascular diseases, which is related to atherogenic dyslipidemia. Atherogenic dyslipidemia refers to the high levels of triglycerides (TG) and small-dense low-density lipoprotein cholesterol (LDL) and low levels of high-density lipoprotein (HDL) [1]. da Luz et al. [2] showed that ratio of TG to HDL has the strongest association with coronary disease. These ratios correlate inversely with atherogenic

✉ Department of Biochemistry, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta 55281; *corresponding author e-mail*: nartyr@ugm.ac.id

index that calculated as log TG/HDL [3]. In diabetic patients, non-HDL cholesterol can be a predictor of cardiovascular disease than is more powerful than LDL cholesterol or triglycerides [4]. Nimmanapalli et al. [5] and Zabeen et al. [6] reported that non-HDL cholesterol levels and atherogenic coefficient in T2DM patients were higher than controls. Non-HDL cholesterol provides an index of all atherogenic, and is calculated as total cholesterol minus HDL cholesterol [4]. Zhan et al. [7] investigated the state of lipid-driven inflammatory and found that atherogenic index of plasma (AIP) and neutrophil–lymphocyte ratio (NLR) were higher in acute coronary syndrome. These results suggest that atherogenic dyslipidemia can induce inflammation.

Assessing C-reactive protein (CRP) levels is the most practical way to identify inflammation. High CRP levels are found in most individuals with impaired glucose regulation, high values of body mass index (BMI) and waist circumference, which are positively related to the incidence of diabetes. CRP is an inflammatory marker produced and released by the liver under cytokine stimulation such as tumor necrosis factor and interleukin 1 and 6 [8]. Our previous study showed that diabetic rats injected with nicotinamide and streptozotocin have significantly higher CRP levels than in normal rats [9]. Increased levels of CRP in uncontrolled diabetic subjects were significantly higher than in controlled diabetes, which was significantly associated with an increase in HbA1c levels [10,11].

High-fiber diets have been reported to reduce HbA1c and TG levels [11,12] increase HDL-c levels [13] and improve an atherogenic dyslipidemia. A complex and unrefined carbohydrate diet with an emphasis on fibers (14g/1000 calories consumed daily) is recommended for individuals with or at risk for metabolic syndrome [14]. Dietary fibers including resistant starch are not digested in the small intestine but can be fermented by the colonic bacteria to produce short chain fatty acids (SCFAs), mainly acetic acid, propionic acid and n-butyric acid [15]. The SCFAs, in particular propionic and butyric acids have been reported as anti-inflammatory [7]. Complex of SCFAs-receptor has anti-inflammatory, anti-obesity, and anti-diabetic effects [8]. Therefore, this study evaluated the effect of fiber-rich snack on CRP levels and atherogenic index in T2DM patients.

## Material and method

### *Subjects*

T2DM patients, aged 40-60 years recruited from the Polyclinic of Internal Medicine (Endocrine), General Hospital Dr. Sardjito, Yogyakarta, Indonesia. Previous research subjects have been diagnosed with T2DM for at least 1 year. Their fasting blood glucose (FBG) was over than 126 mg/dL, and they were treated with oral antidiabetic agents or insulin. Exclusion criteria were smoking, pregnancy or lactation, and blood pressure > 140/90 mmHg. This study was conducted with guidance set out in the Helsinki Declaration. The procedures and informed consent have been approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta (Ref: KE/FK/073/EC/2015). Written informed consent was obtained from all patients. Twenty patients were included in this study.

### *Intervention*

The subjects receive detailed written and oral instructions from an experienced dietician for their diet, including the quantity and quality of food products consumed. They are advised to consume an average daily energy intake of 1500 kcal, and to meet the diet. Monitoring was done

with 3 days food record. They also received a 32g daily snack made of a mixture of *Dioscorea esculenta*, arrowroot, cassava and pumpkin containing 150 kcal, and given for 4 weeks. A total of 100g snacks contains 3.02g protein, 18.23g fat, 59.03g carbohydrate, 4.81g soluble fiber, 14.91g insoluble fiber include 13.26g resistant starch, as well as 484.86 kcal.

*Biochemical analysis*

To obtain plasma, the EDTA blood sample was centrifuged at 3000 g for 15 min at room temperature. EDTA-plasma is used to determine lipid profiles, CRP, and HbA1c. Lipid profiles were analyzed enzymatically using commercial kit (Diasys, Holzheim, Germany). CRP (DRG, International Inc, USA) and HbA1c (Elabscience, WuHan, P.R.C) were analyzed using the ELISA method. All analytical procedures are carried out in accordance with the manufacturer's protocol.

*Statistical analysis*

All parameters were measured twice, before and after consuming fiber-rich snacks. The paired sample *t* test is used to analyze the normal distributed data and the Wilcoxon signed-rank test to analyze abnormal distributed data. The difference was statistically significant at $p < 0.05$.

## Results

*Anthropometric parameters*

A total of 20 diabetic patients, 6 men and 14 women, aged 52.5 ± 3.46 years were included in the study. Anthropometric subjects before and after treatment are presented in Table 1.

**Table 1.** Changes in anthropometry of subjects before and after consuming fiber-rich snacks.

| Anthropometric parameters | Before | After | Mean difference | Paired *t* Test (p) |
|---|---|---|---|---|
| Weight (kg)* | 71.45 (59.60-105.50) | 70.50 (58.90-107.00) | - 0.64 | 0.034 |
| BMI (kg/m$^2$) | 28.72 ± 3.23 | 28.43 ± 3.18 | -0.29 | 0.033 |
| Waist circumference (cm) | 94.31 ± 7.80 | 91.75 ± 7.25 | -2.56 | <0.001 |
| SBP (mmHg) | 127.80 ± 20.75 | 128.25 ± 20.69 | 0.45 | 0.892 |
| DBP (mmHg) | 79.15 ± 11.85 | 83.00 ± 11.10 | 3.85 | 0.168 |

BMI= body mass index; SBP= systolic blood pressure; DBP= diastolic blood pressure.
*Values are presented as median (min-max), $p<0.05$ according to Wilcoxon test.

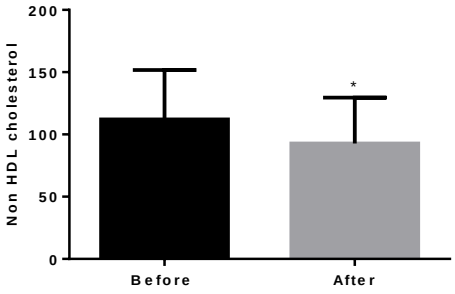


**Figure 1.** *Non-HDL cholesterol levels (mg/dL) before and after consuming fiber-rich snancks.*

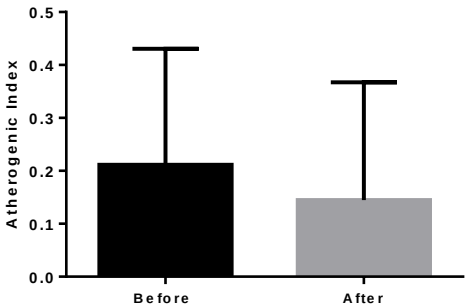


**Figure 2.** *Atherogenic index before and after consuming fiber-rich snacks.*

After consuming fiber-rich snacks for 4 weeks, weight, BMI, and waist circumference were significantly reduced, although blood pressure remained unchanged.

*Lipid profile, HbA1c and CRP levels*

Four-week fiber-rich snack interventions in T2DM patients decreased levels of non-HDL

cholesterol (Figure 1) and atherogenic index although was not significant (Figure 2).

The intervention also reduces CRP levels, but it does not affect HbA1c levels (Table 2).

**Table 2.** *Biochemical changes of the subjects before and after consuming fiber-rich snacks.*

| Biochemical parameters | Before | After | Mean difference | Paired *t* Test (p) |
|---|---|---|---|---|
| CRP (mg/L) | 0.227 (0.031 – 0.737) | 0.179 (0.036 – 0.276) | - 0.129 | 0.044 |
| HbA1c (19) (ng/mL) | 39.79 (17.76 – 47.74) | 40.22 (9.78 – 47.57) | 0.43 | 0.376 |

HbA1c= Hemoglobin A1c; CRP= C-reactive protein. Values are presented as as median (min-max), $p<0.05$ according to Wilcoxon test.

## Discussion

Insulin resistance in T2DM stimulates the mobilization of free fatty acid from adipose tissue, which causes dyslipidemia. Diabetic dyslipidemia is characterized by elevated TG, decreased HDL, and high of small dense LDL particles [16]. The TG/ HDL ratio is inversely correlated with the atherogenic index calculated as logTG/HDL [3]. Increased atherogenic risk was associated with a non-HDL cholesterol increase, the most preferred atherogenic lipoprotein and non-HDL cholesterol has been suggested by the adult treatment panel III of national cholesterol education program (NECP) as a therapeutic goal for diabetic patients [17]. Nimmanapalli et al. [5] and Zabeen et al. [6] reported that non-HDL cholesterol and atherogenic coefficient in T2DM patients were higher than controls.

Fiber has been known to have an effect on improve lipid profile and a diet rich in fiber with a low glycemic index (GI)/low glycemic load (GL) may be recommendable in patients with T2DM [18]. Eating at least 22 g/day fiber may reduce total cholesterol and LDL in healthy premenopausal women, and estradiol may slightly reduce the effect [19]. In the gastrointestinal tract, dietary fibers can trap cholesterol and excrete it in feces. Therefore, cholesterol is diverted to bile acid synthesis, and less cholesterol is passed to the liver via chylomicron remnants and resulting in low hepatic cholesterol pools [20]. Our results showed that supplementing 32g of fiber-rich snacks made of *Dioscorea esculenta*, arrowroot, cassava and pumpkin for 4 weeks reduced non-HDL cholesterol and atherogenic index in T2DM patients. A total of 100g snacks contain 3.02g protein, 18.23g fat, 59.03g carbohydrate, 4.81g soluble fiber, 14.91g insoluble fiber include 13.26 g resistant starch, which energizer 484.86 kcal. Non-HDL cholesterol contains all apoB containing lipoproteins in blood that mediates atherogenesis. These lipoproteins enter the arterial wall and undergo oxidative modification and then contribute to atherogenesis [21]. Therefore, reducing non-HDL cholesterol lowers atherogenic index.

Snack supplementation also significantly reduces body weight, BMI, and waist circumference of the T2DM patients. Fiber has a bulking effect that enhances a sense of “fullness”, [22] which reduce energy intake and stimulate the body to use energy stored through lipolysis. Jensen et al. [23] showed that supplementation of sodium alginate fiber for 12 weeks increased weight loss and improved body composition in obese subjects. Loss of weight, BMI, and waist circumference may reduce inflammatory of T2DM patients. Obesity, overweight and waist circumference are strongly associated with a strong increase in CRP in adults [24]. High CRP levels are positively associated with incident of diabetes [25,8]. In this study, fiber-rich snacks were able to reduce the CRP levels but did not alter the HbA1c

levels. No effect of fiber-rich snacks in the HbA1c levels may be due to limited intervention time. The HbA1c is used to indicate chronic glycaemia that gives an integrated index of glycaemia in 120 days [26]. The decreased CRP levels in the study was consistent with study conducted in Sweden, which showed that fiber-rich products with 10.7g soluble fiber per day reduce significantly CRP levels [27]. A randomized and controlled crossover study with a high fiber diet group (28g total dietary fiber per day) and a fiber-supplemented group (psyllium, 26g total dietary fiber per day) for 3 weeks significantly reduced CRP levels by -13.7 % and -18.1 % in each group, respectively [27].

## Conclusions

The fiber-rich snack has a positive effect in improving non-HDL cholesterol, atherogenic index and CRP levels but does not affect HbA1c levels in T2DM patients.

***Acknowledgements***. This study supported by Ministry of research, technology, and higher education Republic of Indonesia.

## REFERENCES

**1. Manjunath CN, Rawal JR, Irani PM, Madhu K**. Atherogenic dyslipidemia. *Indian J Endocrinol Metab* 17(6): 969-976, 2013.

**2. da Luz PL, Favarato D, Junior JRF-N, Lemos P, Chagas ACP**. High ratio of triglycerides to HDL cholesterol predicts extensive coronary disease. *CLINICS* 63(4): 427-432, 2008.

**3. Suchitra MM, Sheshu KM, Bitla AR, Madhusudhana RA, Alok S**. Atherogenic dyslipidemia in diabetic nephropathy: lipoprotein (a), lipid ratios and atherogenic index. *Int J Res Med Sci* 1:455-459, 2013.

**4. Peters AL**. Clinical relevance of non-hdl cholesterol in patients with diabetes. *Clinical Diabetes* 26(1): 3-7, 2008.

**5. Nimmanapalli HD, Kasi AD, Devapatla PK, Vani Nuttakki V**. Lipid ratios, atherogenic coefficient and atherogenic index of plasma as parameters in assessing cardiovascular risk in type 2 diabetes mellitus. *Int J Res Med Sci* 4(7): 2863-2869, 2016.

**6. Zabeen S, Rahman MR, Mustafa TG, Eusufzai NH, Shermin S**. Non-HDL cholesterol and type 2 diabetes mellitus. *AKMMC J* 3(2): 15-18, 2012.

**7. Zhan Y, Xu T, Tan X.** Two parameters reflect lipid-driven inflammatory state in acute coronary syndrome: atherogenic index of plasma, neutrophil–lymphocyte ratio. *BMC Cardiovascular Disorders* 16: 96, 2016.

**8. Wang Z, Hoy WE**. C-reactive protein and the risk of developing type 2 diabetes in Aboriginal Australians. Diabetes Research and Clinical Practice (in press). *Diabetes Res Clin Pract* 76: 37-43, 2007.

**9. Sunarti, Nurliyani, Tyas ASA, Kristian SD, Prasetyastuti**. The influence of goat milk and soybean milk kefir on il-6 and crp levels in diabetic rats. *Rom J Diabetes Nutr Metab Dis* 22: 261-267, 2014.

**10. Sarinnapakorn V, Wanicagool W**. Association between hs-CRP and Hba1c in overweight type 2 diabetic female patients. *J Med Assoc Thai* 96: 54-8, 2013.

**11. Velázquez-López L, Muñoz-Torres AV, García-Peña C, López-Alarcón M, Islas-Andrade S, Escobedo de la Peña J.** Fiber in Diet Is Associated with Improvement of Glycated Hemoglobin and Lipid Profile in Mexican Patients with Type 2 Diabetes. *J Diabetes Res* 2016: 1-9, 2016.

**12. Jiang J, Qiu H, Zhao G, et al**. Dietary Fiber Intake Is Associated with HbA1c Level among Prevalent Patients with Type 2 Diabetes in Pudong New Area of Shanghai, China. *PLoS One* 7(10): 46552, 2012.

**13. Zhou Q, Wu J, Tang J, Wang JJ, Lu CH, Wang P**. Beneficial Effect of Higher Dietary Fiber Intake on Plasma HDL-C and TC/HDL-C Ratio among Chinese Rural-to-Urban Migrant Workers. *Int J Environ Res Public Health* 12(5): 4726-38, 2015.

**14. Kaur JA**. Comprehensive Review on Metabolic Syndrome. *Cardiology Research and Practice* 2014: 1-21, 2014.

**15. Fuentes-Zaragoza E, Riquelme-Navarrete MJ, Sánchez-Zapata E, Pérez-Álvarez J**. Resistant starch as

functional ingredient: A review. *Food Res Int* 43(2010): 931–942, 2010.

**16. Palazhy S, Viswanathan V**. Lipid Abnormalities in Type 2 Diabetes Mellitus Patients with Overt Nephropathy. *Diabetes Metab J* 41(2): 128–134, 2017.

**17. Abbasi MA, Hafeezullah, Shah NA, Abro A-u-D, Sammo JA**. Non high density lipoprotein cholesterol in type 2 diabetes mellitus. *Pak J Physiol* 3: 1-4, 2007.

**18. Jung C-H and Choi KM**. Impact of High-Carbohydrate Diet on Metabolic Parameters in Patients with Type 2 Diabetes. *Nutrients* 9: 1-21, 2017.

**19. Mumford SL, Schisterman EF, Siega-Riz AM, Gaskins AJ, Wactawski-Wende J, VanderWeele TJ**. Effect of dietary fiber intake on lipoprotein cholesterol levels independent of estradiol in healthy premenopausal women. *Am J Epidemiol* 173(2): 145-56, 2011.

**20. Galisteo M, DuarteJ, Zarzuelo A**. Effects of dietary fibers on disturbances clustered in the metabolic syndrome. *J Nutr Biochem* 19(2): 71-84, 2008.

**21. Chowdhury S, Chowdhury JR, Goswami S**. The importance of non high density lipoprotein cholesterol in dyslipidemia management. *J Diabetes Metab* 6(11): 1-5, 2015.

**22. Perry JR, Ying W**. A review of physiological effects of soluble and insoluble dietary fibers. *J Nutr Food Sci* 6: 1-6, 2016.

**23. Jensen MG, Kristensen M, Astrup A**. Effect of alginate supplementation on weight loss in obese subjects completing a 12-wk energy-restricted diet: a randomized controlled trial. *Am J Clin Nutr* 96(1): 5–13, 2012.

**24. Choi J, Joseph L, Pilote L**. Obesity and C-reactive protein in various populations: a systematic review and meta-analysis. *Obes Rev* 14: 232-44, 2013.

**25. Pitsavos C, Tampourlou M, Panagiotakos DB, et al.** Association Between Low-Grade Systemic Inflammation and Type 2 Diabetes Mellitus Among Men and Women from the ATTICA Study. *Rev Diabet Stud* 4(2): 98–104, 2007.

**26. Florkowski C**. HbA1c as a Diagnostic Test for Diabetes Mellitus – Reviewing the Evidence. *Clin Biochem Rev* 34(2): 75–83, 2013.

**27. King DE, Egan BM, Woolson RF, Mainous AG III, Al-Solaiman Y, Jesri A**. Effect of a high-fiber diet vs a fiber-supplemented diet on C-reactive protein level. *Arch Intern Med* 167(6): 502–6, 2007.