Associations between Dietary Pattern, Bioactive Algal Nutrients Supplementation and Metabolic Risk Markers in Japanese Women: The NAMI Pilot Study

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Abstract: Unhealthy diet can lead to the development of metabolic disorders, and studies have shown strong associations between those conditions, c-reactive protein (CRP) and adiponectin. We report on associations between metabolic markers and bioactive nutrients from diet and Sujiaonori algal biomaterial (SBM), a natural adiponectin modulation inducer (NAMI) containing 60% of bioactive ulvan-rich fiber, in a sample of Japanese women. The study comprised dietary survey and intervention conducted in Kochi, Japan (2016-2017), involving 31 women who completed a dietary survey and provided biospecimen for CRP and adiponectin measurement using ELISA. Sixteen women received 3g SBM daily for one month and 15 others (controls) received 3g of corn starch. In SBM group, mean age was 23.06 (2.21) years [vs. 23.06 (1.55)], BMI was 21.11 (0.59) kg/m^2 [vs. 21.43 (0.60) in controls], and daily intake of n3-PUFA [3.83 (0.24) vs. 2.21 (0.33) mg/day; $p=0.042$] and total fiber [364.12 (2.45) vs. 48.13 (1.57) mg/day in controls; $p=0.000$] were markedly higher. Furthermore, CRP was inversely associated with total fiber, total n3-PUFA, SBM-n3PUFA, vitamin D and vitamin B6, whereas adiponectin was strongly and positively associated with SBM-fiber and total n3-PUFA. Thus ulvan-rich SBM supplement, which contains ulvan-rich fiber and n3-PUFA, might be beneficial in reducing metabolic risk.

Keywords: *Adiponectin; Adiponectin modulation inducer; C-reactive protein; Metabolic marker; Sujiaonori.*

1. Introduction

The global burden of diet and lifestyle-related noncommunicable diseases (NCDs) is impacting the health and productivity in almost all countries [1]. Nutritional pattern of individuals supports their daily physiological needs in nutrients for growth, development and appropriate cell/tissue turnovers [2]. A healthy diet provides necessary energy and nutrients needed to sustain, build and repair the body, and the food that supply them may impact human health either positively or negatively depending on the quality and quantity of food intakes.

It is well-established that a poor nutrition or low-quality food consumption exposes people to the risk of chronic conditions, such as cardiovascular diseases (CVD), obesity, metabolic syndrome, diabetes, and cancer [3, 4]. A study on the primary prevention of coronary heart disease showed that women who practiced a healthy diet and lifestyle pattern were 80% less likely to develop CVD [5]. Furthermore, assessing dietary nutrient intakes, as well as biological markers, might help to analyze physiological and pathological responses to diet and lifestyle patterns, identify subjects with nutritional deficiency and/or at risk of disease and, eventually, suggest dietary recommendations to restore optimal health status [2].

In addition to well-known cardiometabolic health markers, namely systolic blood pressure (SBP), diastolic blood pressure (DBP), circulating cholesterol level, fasting blood glucose (FBG), body weight, waist circumference (WC), etc. [6], recent investigations have demonstrated that circulatory c-reactive protein (CRP) [7-9] and adiponectin [10-13] are strong predictors of most prevalent cardiometabolic diseases such as metabolic syndrome (MetS), diabetes, hypertension, coronary heart disease and atherosclerosis, and play a crucial role in their development. CRP has been suggested as an independent marker of cardiovascular diseases and a number of metabolic disorders, diabetes mellitus in particular [14, 15]. A study by Oda and Kawai [16] conducted in a sample of Japanese men and women during their hospital visits for health screening tests showed a stable and strong correlation between CRP level and MetS more importantly in women, suggesting that CRP could be used as an inflammatory component of this metabolic disorder.

The present pilot study evaluated (1) daily dietary macro and micronutrients intake, their effects on a number of metabolic markers, and (2) the impact of dietary intake of Sujiaonori algal biomaterial (SBM) on adiponectin production in a sample of Japanese women. The second component of this study has been partially published previously [12]. Hereby, we report findings on the effects of bioactive nutrients from the diet and algal supplement on CRP, adiponectin production, BMI and systolic/diastolic blood pressure (SBP, DBP) in a sample of apparently healthy Japanese women.

2. Results

2.1. Sociodemographic characteristics, dietary pattern and macro and micronutrients intake

All women were nonsmokers. Mean age was similar in both study groups, 23.06 (2.21) years in SBM and 23.06 (1.55) in the control group. In SBM group, BMI was 21.11 (0.59) kg/m^2 (vs. 21.43 (0.60) in controls), daily energy intake was 1,371.9±425.4 kcal (vs. 1,356.12±397.31 in controls). Regarding daily intake of macronutrients, SBM group had markedly higher amount of n3 PUFA [SBM-n3PUFA: 3.24 (0.14), 95%CI: 1.99 - 3.61 vs. 1.34 (0.29), 95%CI: 1.21 - 2.98 in controls; p=0.000] and fiber [SBM-fiber: 364.12 (2.45), 95% CI: 358.89 - 369.35 vs. 33.13 (1.57), 95%CI: 19.75 - 36.51; p=0.000] as compared with controls. The later had a higher intake of cholesterol than SBM group [cholesterol: 236.68 (19.14), 95%CI: 175.3 - 258.04 vs. 204.31 (38.5), 95%CI: 201.69 - 446.9 mg/day in SBM group; p=0.031] (**Table 1**).

In addition, when comparing both groups according to daily intake of other macronutrients (protein of animal source, protein of plant source, n6-PUFA) and micronutrients (vitamin B6, vitamin B12, vitamin C, vitamin D, folates, α-tocopherol), the difference did not reach statistical significance, as shown in **Table 1**.

Table 1. Demographic, clinical characteristics and dietary patterns of participants

Variables	Control		SBM group		p
	Mean (SD)	95% CI	Mean (SD)	95% CI	
Clinical parameters					
Age (years)	23.06 (1.55)	19.74 - 26.39	23.06 (2.21)	18.33 - 27.78	0.499
BMI (kg/m^2)	21.43 (0.60)	20.14 - 22.73	21.11 (0.59)	19.84 - 22.3	0.353
Diastolic BP (mmHg)	73.26 (1.35)	70.35 - 76.17	73.5 (1.34)	70.63 -76.36	0.451
Systolic BP (mmHg)	110.53 (2.09)	105.04 -114.02	109.68 (2.04)	103.92-112.25	**0.046**
Nutrients intake/day					
Vitamin B6 (mg/day)	1.07 (0.18)	0.69 - 1.46	0.781 (0.08)	0.59 - 0.97	0.08
Vitamin B12 (g/day)	9.43 (2.6)	3.84 - 15.01	4.74 (0.46)	3.73 - 5.75	0.055
Vitamin C (mg/day)	86.74 (18.49)	57.08 - 136.40	85.31 (9.23)	87.17 - 135.44	0.166

Vitamin D (mg/day)	13.21 (3.94)	4.75 - 21.67	5.98 (0.59)	4.69 - 17.27	0.058
Total folates (mg/day)	224.44 (50.35)	176.43 - 392.44	215.66 (23.8)	163.77-267.56	0.125
α-tocopherol (mg/day)	6.02 (0.74)	4.42 - 7.61	6.22 (0.49)	3.94 - 6.11	0.145
Total n3 PUFA (g/day)	2.21 (0.33)	1.49 - 2.63	3.83 (0.24)	2.01 - 3.89	**0.000**
SBM-n3PUFA (g/day)	-	-	3.24 (0.14)	1.99 - 3.61	-
Control-n3PUFA (g/day)	1.34 (0.29)	1.21 - 2.98	-	-	-
Total n6 PUFA (g/day)	7.8 (0.83)	6.015 - 9.61	7.25 (2.12)	3.84 - 9.85	0.139
Total fiber (mg/day)	48.13 (1.57)	9.75 - 16.5	224.29 (32.06)	128.82 - 285.8	**0.000**
SBM-fiber (mg/day)	-	-	364.12 (2.45)	358.9 - 369.35	-
Control-fiber (mg/day)	33.13 (1.57)	19.75 - 36.51	-	-	-
Total plant protein (g/day)	18.98 (3.15)	12.21 - 25.74	23.41 (1.77)	19.56 - 27.25	0.124
Animal protein (g/day)	29.918 (3.8)	21.75 - 38.08	23.45 (2.58)	17.87 - 29.03	0.088
Cholesterol (mg/day)	236.68 (19.14)	175.3 - 258.04	204.31 (38.5)	201.69 - 446.9	**0.031**

**Notes: CI, confidence interval; BP, blood pressure; n3-PUFA, omega-3 polyunsaturated fatty acid; n6 PUFA, omega-6 polyunsaturated fatty acid; SD, standard deviation; SBM, sujiaonori biomaterial-based supplement.*

2.2. Relationship between diet/intervention-provided bioactive nutrients and metabolic markers (CRP, adiponectin, blood pressure, BMI)

The linear regression analysis showed inverse associations between CRP and vitamin B6 [β= -12.8 (6.71), 95%CI: -22.91 - 201.81; p=0.0023], CRP and vitamin D [β= -149.5 (10.58), 95%CI: -267.31 - 32.69; p=0.033], CRP and SBM-n3PUFA [β= -65.82 (2.81), 95%CI: -187.94 - 174.24; p=0.048].

In contrast, adiponectin was positively associated with vitamin D [β= 3.69 (2.95), 95%CI: 3.42 - 17.81; p=0.034], adiponectin with SBM-n3PUFA [β= 5.96 (5.06), 95%CI: 1.51 - 18.42; p=0.038] and between adiponectin and SBM-fiber [β= 10.51 (1.79), 95%CI: 5.79-18.23; p=0.005] (**Table 2**).

Furthermore, regarding BP profile of the study participants, SBP was inversely associated with total SBM-n3PUFA [b= -3.98 (5.05), 95%CI: -12.83 - 8.86; p=0.046]. However, no association was found between DBP and any of the macro and micro nutrients that were considered in the data analysis; the same was true for BMI (not shown).

Table 2. Associations between metabolic markers (CRP. adiponectin) and intake of bioactive nutrients

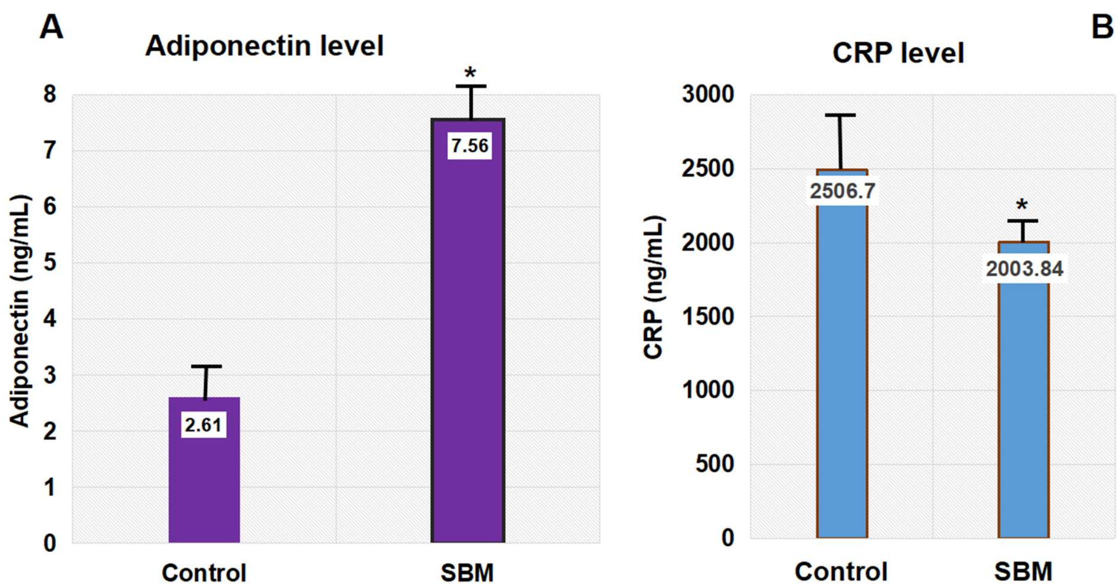
Independent variables	CRP			Adiponectin		
	β (SE)	95% CI	p	β (SE)	95% CI	p
Vitamin B6	-12.8 (6.71)	-22.91 – 201.81	**0.023**	0.14 (0.13)	-.013 - 1.04	0.293
Vitamin B12	31.45 (10.27)	26.78 – 60.12	0.135	-7.88 (6.57)	-13.98 – 8.26	0.276
Vitamin C	-8.79 (2.27)	-81.74 – 64.15	0.755	1.43 (0.28)	0.26 – 2.11	0.182
Vitamin D	-149.5 (78.3)	-267.31 – 32.69	**0.033**	3.69 (2.95)	3.42 – 17.81	**0.034**
Folates	2.51 (10.58)	-22.69 – 31.71	0.688	0.65 (0.46)	-0.45 – 1.17	0.205
α–tocopherol	34.32 (20.17)	-159.1 – 228.72	0.283	26.4 (23.95)	-11.78 – 80.5	0.148
Cholesterol	0.05 (0.14)	-0.03 - 0.02	0.971	-1.55 (1.42)	-8.65 - 5.54	0.655
SBM-n3 PUFA	-65.82 (2.81)	-187.94 - 174.24	**0.048**	5.96 (5.06)	1.51 – 18.42	**0.038**
SBM-n6 PUFA	7.41 (4.29)	-2.54 – 17.42	0.112	0.68 (0.33)	-1.46 – 3.95	0.079
SBM-fiber	-25.73 (43.97)	-122.52 - 71.06	0.057	10.51 (1.79)	5.79 - 18.23	**0.005**
Tot. plant protein	-0.11 (0.01)	-0.003 - 0.05	0.313	0.13 (0.06)	-0.54 - 0.57	0.962
Animal protein	2.09 (0.12)	-0.25 - 3.09	0.808	-0.09 (2.22)	-0.57 - 1.37	0.678

**Notes:* CRP, c-reactive protein; SE, standard error; PUFA, polyunsaturated fatty acid.*

3. Discussion

Adipocyte-derived protein adiponectin plays an important role in human physiology and serves as a link among adiposity and cardiometabolic diseases such as type-2 diabetes mellitus (T2DM) and CVDs. Association between hypoadiponectinemia and cardiometabolic diseases (MetS, T2DM, CVDs, etc.) is well-documented [17-20], and many specialists in the field of NCDs suggest that the discovery of adiponectin modulators and/or adipoR agonists could be a big step towards preventing and, eventually, reversing the disease course of adiponectin-associated NCDs [21-25].

The present study showed that daily intake of SBM-contained fiber and n3-PUFA induced the production of adiponectin more efficiently as compared with corn-starch supplemented controls. Moreover, intakes of both nutrients, fiber and n3-PUFA, from marine green alga Sujiaonori-derived supplement were positively associated with adiponectin (**Figure 1A-B**). Sujiaonori grown in river and farms in Kochi prefecture in western region of Japan, is composed of 60-65% fiber, whose main compounds are ulvans; they are sulfated polysaccharides that possess many beneficial nutraceutical properties such as antioxidative, immunostimulating, anticancer, anticoagulant, antiviral and antihyperlipidemic activities [12, 26-27]. Our experimental study also showed that ulvan from marine alga Sujiaonori has exerted an anti-inflammatory activity that revealed to be better than that of other marine algae growing in the region [28].



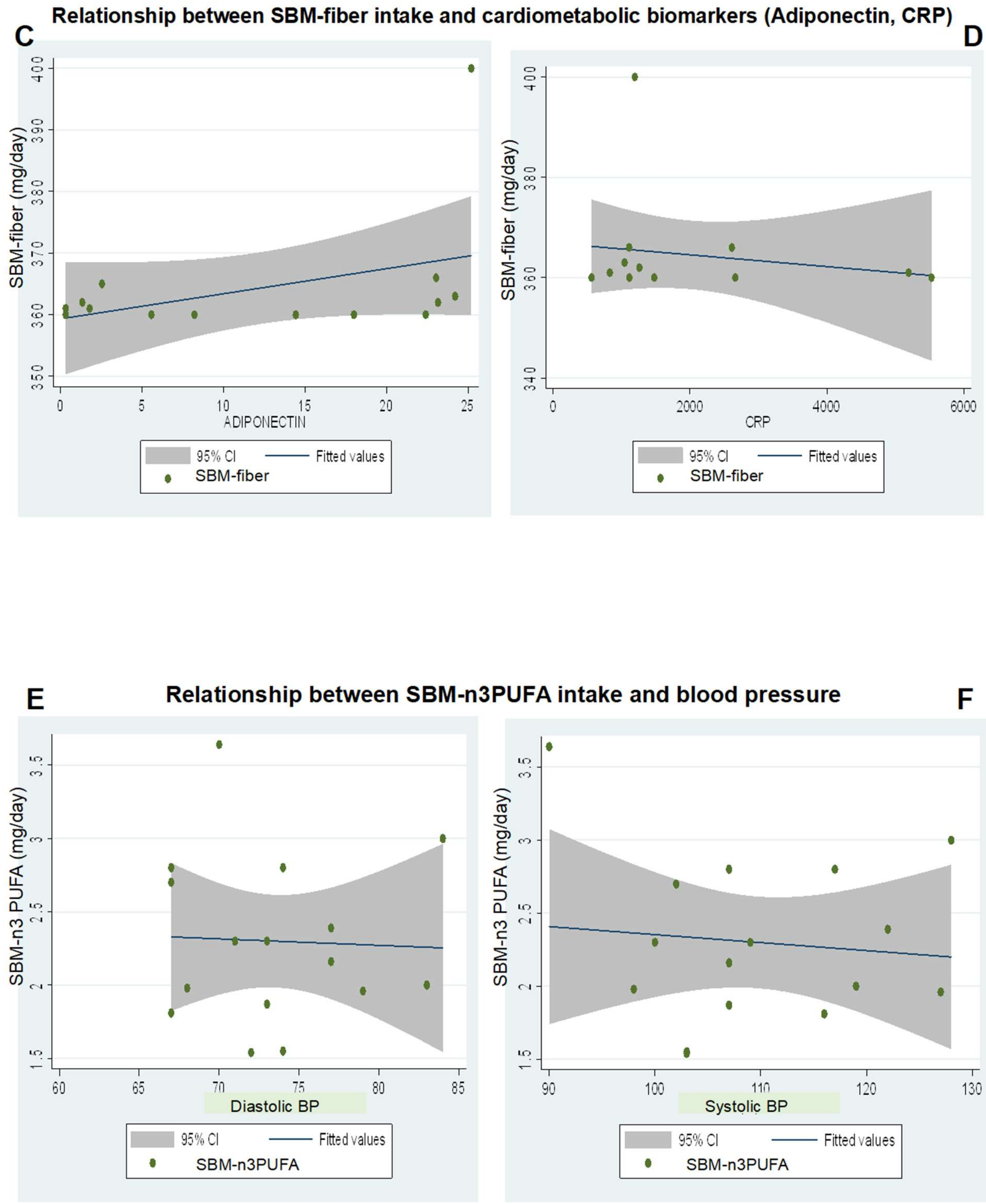


Figure 1. Distribution of mean adiponectin and CRP levels in study groups (A, B) and graphs showing the linear relationship between intake of fiber and metabolic markers (C, D), and also between intake of n3-PUFAs and blood pressure profile (E, F) in SBM-supplemented women.

The figure shows that intake of SBM supplement increased adiponectin (A), while reducing CRP (B) in Japanese women. Additionally, linear relationship was observed between intake of fiber from SBM and adiponectin going crescendo (C) and CRP going decrescendo (D), whereas linear relationship between n3-PUFAs and BP (DBP, SBP) going decrescendo (E, F) in SBM group.

Furthermore, the association between adiponectin and PUFA has also been reported previously. Meta-analysis studies focusing on clinical trials related to adiponectin modulating effect of PUFAs in diabetic patients have shown concluded that n3-PUFAs such as EPA and DHA or their combination increase adiponectin production [29-30]. Thus, considering those reports and our findings (**Figure 1C-F**), it is noteworthy that SBM could, at least partially, improve BP profile thanks to its adiponectin modulating activity, resulting probably from the combined effects of SBM fiber and n3-PUFAs.

This study did not explore the mechanisms underlying the adiponectin modulating activity of SBM. Experimental and clinical investigations that would elucidate those mechanisms and efficacy of SBM-based supplements are currently underway using animal model of obesity, T2DM and human subjects suffering from T2DM.

Despite the above-mentioned limitation, findings from this study provide a new understanding and scientific insights on the beneficial effects of SBM on metabolic health, as well as its potential to prevent and, possibly, reverse adiponectin-associated metabolic disorders.

4. Methods

4.1. Study design and sample size

This was a mixed method study conducted in Kochi prefecture, Japan, between 2016 and 2017. Inclusion criteria have been described previously [12]. Briefly, participants were university undergraduate students and staff from Kochi prefecture who voluntarily accepted to take part in this study. Inclusion criteria were as follows: 20 years of age or older, absence of any known major health condition, and provision of signed informed consent form.

The study included a cross-sectional design consisting in a dietary survey, and a dietary intervention. Clinical examination of the participants was performed and vital signs were monitored at baseline and end of study. In addition, saliva sampling was carried out for the measurement of targeted bio markers associated with metabolic health, namely CRP and adiponectin. Of the 40 enrolled subjects, only data from 31 women who completed a dietary survey, underwent baseline and end-of-study clinical examination and biospecimen sampling were considered in the statistical analysis.

4.2. Diet history survey

A dietary questionnaire is a useful assessment tool of long-term dietary habit and food culture which often vary by community and country. The brief self-administered diet history questionnaire (BDHQ) was used in this study. It is a validated 58-item fixed-portion-type questionnaire that has been developed at the University of Tokyo for assessment of Japanese diets [31, 32]. The questionnaire uses the list of food and beverage items contained in the Japanese National Health and Nutrition Survey [33]; it comprises 102 questions on food items portion size and beverage items during the preceding month by considering the following five sections:

(1) Frequency of food and nonalcoholic beverage items;

(2) Daily rice and miso soup intake;

(3) Frequency of drinking and the amount per drink for alcoholic beverages;

(4) Cooking methods and,

(5) General dietary behavior.

The crude values of energy and 42 selected nutrients are estimated based on the intake of food items were obtained, with the use of a purpose-built computer algorithm based on standard tables of Food Consumption in Japan [34, 35].

4.3. Enzyme-linked immunosorbent assay (ELISA) for measurement of bio markers

Bio markers (CRP, adiponectin) were measured in saliva samples with the use of procedures described previously [12]. Briefly, at least 60 minutes prior to brushing teeth or drinking/eating in the morning, 5 mL of whole saliva was collected in prepared tubes with funnel, at the biochemical laboratory of the graduate school of Nutrition, University of Kochi, Japan. After saliva sampling, the test tube was immediately put on ice and then stored at -20°C in the laboratory. Bio markers were assayed using Human adiponectin and C-reactive protein ELISA kits (AssyPro, St Charles, MO, USA) following the manufacturer's instructions. These assays were performed in duplicate.

4.4. Data collection and analysis

Dietary survey data were managed by an independent research center that estimated values of amount of energy/nutrients using a diet history software. Values of metabolic markers are expressed as means and standard deviations. For continuous variables, linear regression analysis was performed to assess the association between metabolic markers (BMI, SBP, DBP, CRP, adiponectin) and the intake of bioactive macro and micronutrients from both diet and supplements. Data analysis was performed using Stata statistical software version 15 (Stata Corp., College Station, TX, USA). P-values less than 0.05 were considered significant.

5. Patents

Patent application was already submitted and is currently accessible online [IP FORCE patent office, Japan; No 2018-58770(P2018-58770A)].

Author contributions

- NRN and MI designed and performed all activities of the study; they also collected, analyzed the data and draft the manuscript.

- TH contributed in the analysis of data included in this paper, as well as drafting and proofreading it.

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Institutional review Board Statement. This study was approved by the Ethics committee of University of Kochi Faculty of Nutrition (Approval No) and ISRCTN international clinical trial registry (No ISRCTN35616776). The funding institution had no role n the study design, data collection, analysis or interpretation.

Informed consent Statement. All participants provided written informed consent prior to being enrolled in this study.

Data Availability Statement. Database of this study can be accessed by a request to the corresponding authors after the related patent is issued

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Conflict of interest. Authors declare no conflict of interest related to this study.

References

1. Karupaiah, T.; Chuah, K.A.; Chinna, K.; Pressman, P.; Clemens, R.A.; Sundram, W.H.K. A cross-sectional study on the dietary pattern impact on cardiovascular disease biomarkers in Malaysia. Sci. Rep. 2019, 9, 13666.

2. Pico, C.; Serra, F.; Rodriguez, A.M.; Keijer, J.; Palou, A. Biomarkers of nutrition and health: new tools for new approaches. Nutrients **2019**, 11(5), 1092.

3. Eyre, H.; Kahn, R.; Robertson, R.M. Preventing cancer, cardiovascular disease, and diabetes: a common agenda for the American Cancer Society, the American Diabetes Association, and the American Heart Association. Diabetes Care **2004**, 27(7), 1812–24.

4. Kachan, D.; Lewis, J.E.; Davila, E.P.; Arheart, K.L.; LeBlanc, W.G.; Fleming, L.F. et al. Nutrient intake and adherence to dietary recommendations among US workers. J. Occup. Environ. Med. **2012**, 54(1), 101–105.

5. Stampfer, M.J.; Hu, F.B.;, Manson, J.E.; Rimm, E.B.; Willett, W.C. Primary prevention of coronary heart disease in women through diet and lifestyle. N. Engl. J. Med. **2000**, 343(1), 16-22.

6. Hruby, A.; Jacques, P.F. Dietary protein and changes in markers of cardiometabolic health across 20 years of follow-up in middle-aged Americans. Publ. Health Nutr. **2018**, 21 (16), 2998-3010.

7. Ridker, P.M.; Buring, J.E.; Cook, N.R.; Rifai, N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events. Circulation **2003**, 107, r20-r26.

8. Pradhan, A.D.; Manson, J.E.; Rifai, N.; Buring, J.E.; Ridker, P.M. C-reactive protein, interleukin 6, and the risk of developing type-2 diabetes mellitus. JAMA. **2001**, 286, 327-334.

9. Freeman, D.J.; Norrie, J.; Caslake, M.J.; Gaw, A., Ford, I.; Lowe, G.D.O.; O'Reilly, D.S.J. et al. C-reactive protein is an independentpredictor of risk for the development of diabetes in the West of Scotland Coronary Prevention Study. Diabetes **2002**, 51, 1596-1600.

10. Maeda, N.; Shimomura, I.; Kishida, K.; Nishizawa, H.; Matsuda, M.; Nagaretani, H. et al. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. Nat. Med. **2002**, 8(7), 731-7.

11. Kandasamy, A.D.; Sung, M.M.; Boisvenue, J.J.; Barr, A.J.; Dyck, J.R.B. Adiponectin gene-therapy ameliorates high fat, high sucrose diet-induced metabolic perturbations in mice. Nutr. Diab. **2012**, 2, e95.

12. Ngatu, N.R.; Ikeda, M.; Watanabe, H.; Tanaka, M.; Inoue, M.; Kanbara, S.; Nojima, S. Uncovering adiponectin replenishing property of sujiaonori algal biomaterial in humans. Mar. Drugs **2017**, 15(2), 32.

13. He, J.; Stryjecki, C.; Reddon, H.; Peralta-Romero, J.; Karam-Araujo, R.; Suarez, F. Adiponectin is associated with cardiometabolic traits in Mexican children. Sci. Rep. **2019**, 9(1), 3084.

14. Ridker, P.M.; Wilson, P.W.F.; Grandy, S.M. Should C-reative protein be added to metabolic syndrome and to assessment of global cardiovascular risk? Circulation **2004**, 109, 2818-20125.

15. Doi, Y.; Wakugawa, Y.; Kiyohara, Y.; Yonemoto, K.; Kubo, M.; Iwase, M. et al. Elevated C-reactive protein is a predictor of diabetes in a general Japanese population; The Hisayama study. Diab. Care. **2005**, 28, 2497-2500.

16. Oda, E.; Kawai, R. Reproducibility of high-sensitivity C-reatice protein as an inflammatory component of metabolic syndrome in Japanese. Circulation J. **2010**, 74, 1488-1493.

17. Hotta, K.; Funahashi, T.; Arita, Y.; Takahashi, M.; Matsuda, M.; Okamoto, Y.; Iwahashi, H. et al. Plasma concentration of a novel adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler. Thromb. Vasc. Biol. **2000**, 20, 1595-1599.

18. Kubota, N.; Terauchi, Y.; Yamauchi, T.; Kubota, T.; Moroi, M.; Matsui. J. et al. Disruption of adiponectin causes insulin resistance and neointimal formation. J. Biol. Chem. **2002**, 277, 25863-25866.

19. Kumada, M.; Kihara, S.; Sumitsuji, S.; Kawamoto, T.; Matsumoto, S.; Ouchi, N. et al. Association of hypoadiponectinemia with coronary artery disease in men. *Arterioscler. Thromb. Vasc. Biol.* **2003**,23, 85–89.

20. Kuo, I.C.; Wu, P.H.; Lin, H.Y.H.; Niu, S.W.; Huang, J.C.; Hung, C.C. et al. The association of adiponectin with metabolic syndrome and clinical outcome in patients with non-diabetic chronic kidney disease. Plos One **2019**, 14(7), e0220158.

21. Wang, Y.; Lam, K.S.L.; Xu, A. Adiponectin as a therapeutic target for obesity-related metabolic and cardiovascular disorders. Drug Dev. Res. **2006**, 67(8), 677-686.

22. Fisman, E.Z.; Tenenbaum, A. Adiponectin: a manifold therapeutic target for metabolic syndrome, diabetes, and coronary disease? Cardiovasc. Diabetol. **2014**, 13,103.

23. Achari, A.E.: Jain, S.K. Adiponectin, a therapeutic target for obesity, diabetes, and endothelial dysfunction. Int. J. Mol. Sci. **2017**, 18(6), 1321.

24. Liu, Y.; Vu, V.; Sweeney, G. Examining the Potential of Developing and Implementing Use of Adiponectin-Targeted Therapeutics for Metabolic and Cardiovascular Diseases. Front. Endocrinol. (Lausanne) **2019**, 10, 842.

25. Ngatu, R.N. Adiponectin modulators: New approach for scaling up noncommunicable diseases (NCDs) prevention and management ? J. International University of Health and Welfare **2019**, 24(2), 73-75.

26. Ngo, D.H.; Kim, S.K. Sulfated polysaccharides as bioactive agents from marine algae. Int. J. Biol. Macromol. **2013**, 62, 70-75.

27. Wang, L.; Wang, X.; Wu, H.; Liu, R. Overview on biological activities and molecular characteristics of sulfated polysaccharides from marine green algae in recent years. Mar. Drugs **2014**, 12(9), 4984-5020.

28. Ngatu, R.N.; Tanaka, M.; Ikeda, M.; Inoue, M.; Kanbara, S.; Nojima S. Sujiaonori-derived algal biomaterials inhibit allergic reaction in allergen-sensitized RBL-2H3 cell line and improve skin health in humans. J. Funct. Biomater. **2017**, 8(3), 37.

29. Farimani, A.R.; Hariri, M.; Azimi-Nezhad, M.; Borji, A.; Zarei, S.; Hooshmand, E. The effects of n-3 PUFAs on circulating adiponectin and leptin in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. Acta Diabetol. **2018**, 55(7), 641-652.

30. Wu, P.; Wen, W.; Li, J.; Xu, J.; Zhao, M.; Chen, H.; Sun, J. Systematic review and meta-analysis of randomized Controlled Trials on the Effect of SGLT2 Inhibitor on Blood Leptin and Adiponectin Level in Patients with Type 2 Diabetes. Horm. Metab. Res. **2019**, 51(8), 487-494.聽

31. University of Tokyo. Dietary assessment method developed in department of social and preventive epidemiology at University of Tokyo. Available from:

http://www.nutrepi.m.u-tokyo.ac.jp/english/dhq/dhq.html

32. Kobayashi, S.; Honda, S.; Murakami, K.; Sasaki, S.; Okubo, H.; Hirota, N.; Notsu, A.; Fukui, M.; Date, C. Both comprehensive and brief self-administered diet history questionnaires satisfactorily rank nutrient intakes in Japanese adults. J Epidemiol **2012**, 22(2), 151-159.

33. Ministry of Health, Labour and Welfare of Japan. The national health and nutrition survey in Japan, 2005. Tokyo: Ministry of Health and Welfare; 2008 (published in Japanese).

34. Agency SaT. Standard Tables of food composition in Japan. 5th rev ed; Tokyo: Printing Bureau of the Ministry of Finance, 2005 (published in Japanese).

35. Toyomaki, A.; Koga, M.; Okada, E.; Nakai, Y.; Miyazaki, A.; Tamakoshi, A. et al. The relationship between a low grain intake dietary pattern and impulsive behaviors in middle-aged Japanese people. Plos One **2017**, 12(7), e0181057.