

Original Article

Could dietary seaweed reverse the metabolic syndrome?

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Incidence of the metabolic syndrome is increasing worldwide, with notable exceptions of some Asian countries where seaweeds are commonly consumed. 13 men (mean age 47.4 ± 9.9 yr) and 14 women (average age 45.6 ± 12.2 yr) with at least one symptom of the metabolic syndrome were recruited in Quito Ecuador to a randomized double-blinded placebo-controlled trial. Subjects were assigned to either Group 1 (1 m placebo, followed by 1 m 4 g/d seaweed [*Undaria pinnatifida*]) or Group 2 (1 m of 4 g/d seaweed, followed by 1 m of 6 g/d of seaweed). Blood pressure, weight, waist circumference, inflammation biomarkers, and lipids were measured monthly. Repeated measures analysis of variance with Tukey's multiple comparison tests were used for statistical analysis. In Group 2, systolic blood pressure decreased 10.5 mmHg after a month of 6 g/d seaweed (95% CI: 4.1, 16.8 mmHg; $p < 0.05$), primarily in subjects with high-normal baseline blood pressure. Waist circumference changed only for women participants, with a 2.4 cm decrease in Group 1 after treatment with placebo (95% CI: 1.0, 3.7 cm; $p < 0.01$). In Group 2, women had a mean decrease of 2.1 cm after 4 g/d (95% CI: 0.4, 3.7 cm; $p < 0.05$) and a further 1.8 cm decrease after 1 m 6 g/d seaweed (95% CI: 0.1, 3.4, $p < 0.05$). No other changes were observed. Consumption of 4 to 6 g/d seaweed, typical for most people in Japan, may be associated with low metabolic syndrome prevalence.

Key Words: seaweed, metabolic syndrome, hypertension, waist circumference, iodine, clinical trial

INTRODUCTION

The metabolic syndrome (MS), a major risk factor for heart disease and stroke as well as a contributor to atherosclerosis, kidney disease, and blindness, is a cluster of symptoms, including obesity, dyslipidemia, hypertension, and glucose dysregulation.¹⁻⁶ As the adoption of Western diets and sedentary lifestyles, along with urbanization and industrialization becomes more common worldwide, so too have death rates risen from diseases associated with MS. The metabolic syndrome is associated with a 1.4-fold increase in all-cause mortality and a 2-fold increase in cardiovascular disease (CVD) mortality.⁷ In a meta-analysis of epidemiologic data, increased systolic blood pressure of 2 mm Hg has been associated with a 10% higher stroke and 7% higher CVD mortality risk.⁸

Not all countries have experienced increased rates of MS. Rates between countries range from 20% in some parts of the world, especially in the West,^{7,9} to only 7% in Japan.¹⁰ The Japanese have the lowest rates of MS and the longest life expectancies in the world.¹¹ CVD mortality rates in Japan are about 30% lower than in the US, and consuming a more traditional Japanese diet, including seaweeds, is associated with this significant CVD protective effect.¹² Specific dietary differences may help explain this. Fish and shellfish consumption in Japan are the highest in the world,¹³ contributing to a high CVD protective omega 3 intake. Additionally, dietary seaweed may play a role in reducing MS. Traditionally people in Japan

have viewed seaweed as both a medicine and as a food.¹⁴⁻¹⁶ *In vitro* and *in vivo* studies of seaweed water extracts have identified 7 specific blood pressure lowering dipeptides with angiotensin converting inhibitory properties.¹⁷⁻²⁰ Seaweed fiber (alginate) gels have also been found to reduce blood pressure, cholesterol, and blood glucose.²¹⁻²³ Interestingly, several mechanisms of action have been proposed for seaweed's hypertensive activity, including the angiotensin-converting-enzyme (ACE) inhibitory action of seaweed dipeptides in lowering blood pressure, physical binding of sodium in the gastrointestinal tract by the acidic polysaccharide fibers (alginate), and calcium channel blocker activity.

Confirmation of the epidemiologic importance of dietary seaweed with regard to MS comes from several lines of evidence. Two observational studies reported that elderly Japanese who consume more seaweed have lower blood pressure,²⁴ and take fewer medications for hypertension than individuals with lower seaweed intakes.²⁵

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Whole seaweed supplements have been used in two clinical hypertension trials, with reduction in systolic blood pressure ranging from 5.7 to 8.0 mmHg,²⁶ and reduced mean blood pressure (MBP) from 111.5 to 101.4 mm Hg.²⁷ Reported effective doses were 3.3 g/d in a Japanese seaweed consuming population,²⁶ and 12 g/d in a Swedish non-seaweed consuming population.²⁷

Central adiposity is required for the diagnosis of MS, and seaweed could also affect waist circumference. Maeda identified a bioactive carotenoid of brown seaweeds, fucoxanthin, as important in reducing lower abdominal adipose tissue weight in obese rats and mice.^{28,29}

In this study we wanted to investigate the importance of brown seaweeds as a dietary supplement that could be useful in modulating the physiological parameters associated with MS in a non-seaweed consuming population in Ecuador. Ecuador has rapidly increasing CVD mortality rates, which have doubled over the past few years; from 10.6/100,000 in 1995 to 20.3/100,000 in 2002.³⁰ Although there are no specific data available on the prevalence of MS in Ecuador, the increase in CVD mortality is most likely due to an increase in the rate of MS, including increased prevalence of hypertension,³¹ hyperlipidemia,^{31,32} obesity,³³ and increased smoking rates.^{32,34,36}

MATERIALS AND METHODS

This study was approved by the Human Subjects Protection Committee at the Universidad San Francisco de Quito, Quito Ecuador. Each participant signed an Informed Consent form after receiving explanation of the study and its possible benefits.

Eligibility criteria

The criteria for MS includes at least three of the following conditions: waist circumference greater than 102 cm for men, greater than 88 cm for women; fasting triglycerides greater than ≥ 150 mg/dL, HDL cholesterol < 40 mg/dL (male), < 50 mg/dL (female); blood pressure greater than 130/85 mm Hg; and fasting glucose greater than 110 mg/dL.³⁷

Participants were screened with regard to blood pressure, waist measurements, blood glucose (with the use of a Cholestech screen), total cholesterol and HDL-cholesterol (Cholestech LDX®, Hayward, CA). Participants with at least one symptom of MS were invited to participate. Using the International Diabetes Federation criteria for MS,³ 14 of the participants met the criteria for MS (large waist plus two of the four other criteria). All 28 participants had at least one of the criteria for MS; People with high blood glucose were excluded (>110 mg/dL).

Participants

Thirty people living in Ecuador with at least one symptom of MS were recruited into the study. One person dropped out of the study (Group 1) because the individual did not like taking so many pills (6 in the morning, 6 in the evening), and one woman (Group 2) was dropped from the analysis because she became pregnant.

Seaweed

Undaria (wakame) is one of the most popular dietary seaweeds eaten in Japan and Korea.³⁸ *Undaria pinnatifida*

(Harv.) Suringar was harvested on January 26, 2006 from Bahia Bustamante on the Patagonian coast of Argentina (Soriano SA). Only the sporophylls of the *Undaria* were used. Standard operating and manufacturing procedures of Soriano SA meet all of the standards of the Argentine government. The *Undaria* was hand harvested by divers, then transported to shore in polypropylene rope bags, hung on fishing nets suspended from iron rafters and shade-dried. The seaweed was completely dry within 24 hours of harvest. The dried seaweed was then wrapped in plastic and stored in cardboard boxes. After milling to a 300 micron powder (done onsite at Gaiman by Soriano SA), the *Undaria* was tested for *Escherichia Coli*, *Salmonella*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, all of which were non-detectable, as well as yeast and mold, aerobic recount, and moisture. It was found to have met all safety standards.[†] Table 1 presents the nutritional and bioactive composition of seaweed.

Placebo

Maltodextrin was provided by Soriano SA for use as placebo and provided 4 calories/g.

Encapsulation

Both the seaweed and placebo were encapsulated in identical gelatin capsules by Vicrofer (Buenos Aires, Argentina). No fillers or binders were added to the seaweed or placebo powder.

Blood pressure measurement

Blood pressure measurements were taken by a research nurse using a Dinamap XL automated BP monitor (Critikon, Tampa FL), and Pan American Health Organization guidelines.³⁹ Three readings were obtained, and two closest readings were averaged for analyses.

Anthropometric measurements

A standardized clinic weight scale was used to determine

Table 1. Nutritional and bioactive composition of *Undaria pinnatifida*

Nutrient	1 g	Reference
Calories	3 cal	Soriano †
Carbohydrates	1 mg	Soriano †
Protein	77 mg	Soriano †
Fat	81 mg	Soriano †
Saturated fat	42 mg	Soriano †
Dietary fiber	49 mg	Soriano †
Soluble fiber	299 mg	Soriano †
Insoluble fiber	72 mg	Soriano †
Sodium	35 mg	Soriano †
Potassium	42 mg	Soriano †
Iron	0.2 mg	Soriano †
Calcium	30 mg	Soriano †
Iodine	39-50 µg	Teas ⁴⁵
Magnesium	3 mg	Soriano †
Bioactive components		
Fucoidan	81 mg/g	Carnachan ⁵¹
Fucoxanthin	2 mg/g	Campbell ⁵⁰
Alginate	15-25 mg/g	Apoya, ⁵⁵ Skriptsova ⁵⁶

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both height and weight of each of the participant at baseline, and then weight at each subsequent visit. Weight and height were taken with participants wearing light clothing, and no shoes. Waist measurements were made using a soft cloth tape measure, with the subject wearing light clothing. With the subject standing, the tape measure was placed mid-way between the lowest rib and the iliac crest, and included the umbilicus. Measurements were recorded at the end of a gentle expiration.⁴⁰ A second measurement was taken and the average of the two measurements was recorded.

Glucose, insulin and homeostasis model assessment-estimated insulin resistance (HOMA)

Serum glucose was measured using a glucose oxidase method (Diagnostic Chemicals Ltd reagent kit). Serum insulin was determined using an electrochemiluminescence immunoassay (ECLIA) following the manufacturer's instructions (Roche/Hitachi, Quito-Ecuador) and the chemiluminescent emission was measured using a fully automated analyzer system ELECSYS 2010 (Roche Diagnostics, Quito - Ecuador).

The HOMA values were calculated using fasting plasma glucose ($\mu\text{mol/l}$) multiplied by fasting serum insulin ($\mu\text{U/l}$) and divided by 22.5.⁴¹

Lipid profile

The Cholestech LDX System® (Hayward, CA) was used for eligibility screening purposes.

A single drop of blood on a disposable test cassette was used to test for total cholesterol, high-density lipoprotein (HDL), and triglycerides.

Total cholesterol, HDL, and triglyceride analyses were measured on a Premier Plus Stanbio Analyzer (Stanbio Laboratory®, Texas, USA) with standard reagents (Cholesterol FS, DiaSys Diagnostic Systems GmbH & Co®; triglyceride reagents Dialine Diagnostic Systems®, Germany).

Serum markers of inflammation (C-reactive protein and nitric oxide)

Nitric oxide in serum was determined by a gas-phase chemiluminescent reaction between NO and ozone.⁴² Briefly, serum samples were mixed with 6% trichloroacetic acid (1:1, v/v) to precipitate the protein; samples were then centrifuged at 610 g for 5 min. Nitric oxide in the supernatants were measured in a Sievers NOA-280 (Boulder, CO).

C-reactive protein was measured using immunoturbidimetric assay with latex particles according to vendor's instructions (Tina-quant CRP [Latex] HS test Roche/Hitachi, Quito-Ecuador). First, the sample was diluted with a Tris buffer solution (pH 7.4), then latex particles coated with a monoclonal anti-CRP specific antibody (mouse) interacted with CRP in the sample in order to cause immune complex agglutination which was measured by turbidimetry in an automated system Hitachi 917 (Roche Diagnostics, Quito-Ecuador).

Iodine content of finished capsules

Iodine in empty capsules and finished capsules were analyzed using the ceric-arsenic redox reaction. Samples

were analyzed according to standard determination of total iodine protocol as outlined by Benotti, et al.⁴⁴ This utilized the reduction-oxidation reaction between ceric and arsenite catalyzed by iodide. The iodine concentration was proportional to its catalytic activity. First iodine was precipitated with perchloric acid and the samples were digested with chloric acid. They were then measured spectrometrically at 420 nm with a Technicon Autoanalyzer (Technicon Instrument, Inc., Tarrytown, NY). Calculations were based on an iodine standard curve. The urine results were calculated as μg iodine/dL, per gram creatinine or total urinary iodine/d. Empty gelatin capsules used in the study were also analyzed for iodine content.

Thyroid stimulating hormone (TSH)

To answer questions about the possibility of iodine content in seaweed as the putative catalyst for change, we analyzed available serum samples after the study for TSH. Samples had been archived at -80° at the University of San Francisco de Quito College of Health Sciences until analysis using an electrochemiluminescence assay (Eclisys 2010, Roche Diagnostics, Quito, Ecuador). Normal value range = 0.27 - 4.2 uU/mL.

Blood samples

Fasting blood samples were taken by a research nurse in the morning between 8 am and 10 am. The samples were centrifuged within 2 hours and aliquoted. All serum samples were stored at -80°C until analysis at the end of the study when they were analyzed by Dr. Manuel Baldeón at his lab in the College of Health Sciences, University of San Francisco de Quito, Quito Ecuador.

Study Design

We used a double-blind crossover study design using 2 groups including one with placebo. Our endpoints were waist circumference, blood pressure, body weight, and blood parameters of glucose, lipids, and anti-inflammation biomarkers. It was our objective to include a dose escalation along with the treatment-placebo crossover design. Subjects were assigned to one of two groups: Group 1: 4 weeks of 5 g/d maltodextrose in 12 identical gelatin capsules (placebo), followed by 4 g/d seaweed (8 seaweed capsules plus 4 placebo capsules) or Group 2: 4 weeks of 4 g/d seaweed powder (8 seaweed capsules plus 4 placebo capsules) followed by 4 weeks of 6 g/d seaweed powder (12 seaweed capsules). The capsules were divided equally between morning and evening, in 7 Day Twice-A-Day Weekly Pill organizers (Apex; Carex Health Brands, Sioux Falls, SD). Six capsules were taken with the first and the last meal each day. The demographic characteristics of participants are presented in Table 2.

Statistical analysis

The original study design involved randomization to Group 1 (one month of placebo followed by one month of supplementation with 4 g/d seaweed) or Group 2 (one month of 4 g/d seaweed followed by one month of 6 g/d seaweed supplementation). In theory this study design would have allowed for comparison of placebo compared

Table 2. Demographics compared by group (Group 1 = Placebo then 4 g/d seaweed; Group 2 = 4 g/d then 6 g/d seaweed)

Demographic characteristic	Group 1 (N = 14)	Group 2 (N = 13)
Gender		
Men	6 (43%)	7 (54%)
Women	8 (57%)	6 (46%)
Age (yr)		
Men	47.2 ± 9.4	45.9 ± 10.3
Women	45.3 ± 11.1	46.5 ± 14.7
Marital status		
Married/living together	12 (86%)	10 (77%)
Divorced/separated	2 (14%)	2 (15%)
Never married	0	1 (8%)
Ethnicity		
Mestizo	14 (100%)	12 (92%)
White	0	1 (8%)
Education		
Primary school (1-6 yr)	2 (14%)	12 (92%)
Secondary School (1-3 yr)	0	6 (46%)
Graduated high school	3 (21%)	2 (15%)
Some college	1 (7%)	1 (8%)
Technical School	0	1 (8%)
Graduated College	6 (43%)	1 (8%)
Masters Degree	2 (14%)	0
Employment		
Housekeeping (work at home)	0	1 (8%)
Services	3 (21%)	6 (46%)
Construction/factory	2 (14%)	3 (23%)
Professional	6 (43%)	2 (15%)
Technical	1 (7%)	0
Unemployed/other	2 (14%)	1 (8%)
Medical history (Previously diagnosed with)		
Cancer (disease free during study)	1 (breast cancer)	0
Hypertension (only)	2 (not on medication)	1 (not on medication)
Hypercholesterolemia (only)	2 (1 on medication)	6 (none on medication)
Hypertension and hypercholesterolemia	5 (2 on medication)	2 (none on medication)
Hypertension, hypercholesterolemia, diabetes	0	2 (1 on medication)
Menopausal symptoms	1 (not on medication)	1 (on medication)
Taking supplements	3 (21%)	3 (23%)
Physical activity		
Intense activity ≥ 2hr/wk	4 (29%)	4 (31%)
Moderate activity ≥ 1 hr/wk	7 (50%)	6 (46%)
None reported	5 (36%)	1 (8%)
Tobacco exposure		
Non-smoker	12 (86%)	9 (69%)
Smoker	2 (14%)	4 (31%)
< 5 cigarettes/d	1 (7%)	3 (23%)
≥ 20 cigarettes/d	1 (7%)	1 (8%)
Family income		
<\$200/m	1 (7%)	3 (23%)
\$200-400/m	3 (21%)	4 (31%)
\$400-600/m	2 (14%)	4 (31%)
\$700-1,000/m	2 (14%)	0
\$1,000-1,500/m	1 (7%)	1 (8%)
\$1,500/m or >	4 (29%)	0
Not given	1 (7%)	1 (8%)

Due to rounding errors, some totals are only 99%

to treatment, and the effect of an escalating dose. One participant was not measured at the end of the study (Group 1). Her information was set to missing and not included in the paired measures analyses, leaving 14 participants in Group 1 and 13 participants in Group 2.

Data were analyzed using GraphPad Software, Inc (GraphPad Prism 5, San Diego, CA); by repeated measures analysis of variance with Tukey's multiple comparison tests to determine differences between baseline and

different treatment periods. Statistical significance was set at $p < 0.05$.

RESULTS

There were no statistically significant differences between the two groups based on demographic or physical characteristics at baseline (Table 2). Although none of the participants had ever been told they had MS, 12 women and 11 men had previously been told they had hyperten-

Table 3. Waist circumference (cm) in healthy adults compared by gender at baseline, after placebo, after 4 g/d seaweed, and after 6 g/d seaweed treatments†

	N	Baseline	Placebo	Low seaweed (4 g/d)	High seaweed (6 g/d)
Group 1 Placebo and Low Seaweed Waist circumference (cm)					
All subjects	14	91.8 (86.8, 96.8)	89.9* (84.7, 95.1)	89.0** (83.7, 94.2)	NA‡
Males	6	95.3 (85.7, 105.0)	94.0 (83.4, 104.6)	93.0 (81.8, 104.2)	
Females	8	89.1 (82.8, 95.5)	86.8* (80.7, 92.8)	86.0** (80.3, 91.7)	
Group 2 Low and High Seaweed Waist circumference (cm)					
All subjects	13	94.2 (89.1, 99.3)	NA‡	92.1 (86.8, 97.4)	91.0 (84.7, 97.3)
Males	7	101.1 (95.0, 107.2)		99.6 (93.9, 105.2)	98.9 (92.4, 105.3)
Females	6	87.3 (84.1, 90.5)		84.7 (81.0, 88.4)	81.8** (77.8, 85.9)

† Values are means (95% CI)

‡ Not applicable

** Significantly different from baseline ($p < 0.01$)*** Significantly different from baseline ($p < 0.001$)**** Significantly different from 4 g/d ($p < 0.01$)**Table 4.** Systolic blood pressure (mmHg) in healthy adults compared by gender at baseline, after placebo, after 4 g/d seaweed, and after 6 g/d seaweed treatments†

	N	Baseline	Placebo	Low seaweed (4 g/d)	High seaweed (6 g/d)
Group 1 Placebo and Low Seaweed					
All Group 1	14	124.2 (117.1, 131.3)	116.8 (110.2, 123.3)	117.8 (109.8, 125.8)	NA‡
High blood pressure (≥ 130 mmHg)	6	136.5 (131.8, 141.2)	123.2* (117.0, 129.3)	128.8 (116.4, 141.3)	
Normal blood pressure (< 139 mmHg)	8	115 (109.7, 120.3)	112.0 (101.7, 122.3)	109.5 (102.3, 116.7)	
Group 2 Low seaweed then high seaweed					
All Group 2	13	128.1 (120.5, 135.7)	NA‡	122.5 (114.1, 130.9)	117.6** (109.9, 125.3)
High blood pressure (≥ 130 mmHg)	8	136.8 (131.4, 142.1)		129.6 (119.2, 140.1)	122.3** (111.0, 133.5)
Normal blood pressure (< 139 mmHg)	5	112.3 (106.6, 118.0)		109.3 (101.5, 117.2)	110.2 (100.3, 120.1)

† Values are means (95% CI)

‡ Not applicable

* Significantly different from baseline ($p < 0.05$)** Significantly different from baseline ($p < 0.01$)

sion, diabetes, or hypercholesterolemia. Medication use was infrequently, with none of the men and only 5 of the women taking medications for any of these conditions.

Waist circumferences of only women decreased during the study (Table 3). These differences were significantly different between baseline and placebo in Group 1 after treatment with placebo (2.3 cm; 95% CI: 1.0, 3.7 cm; $p < 0.01$). Changes between baseline and 4 g/d were also significant (3.1 cm; 95% CI: 1.8, 4.5 cm; $p < 0.001$). For Group 1, there were no further changes between placebo and 4 g/d. In Group 2, women had a mean decrease of 2.7 cm after 4 g/d (95% CI: 1.1, 4.3 cm; $p < 0.01$). Treatment

with 6 g/d was associated with a further 3 cm decrease, which was significant when compared to 4 g/d (95% CI: 1.4, 4.6 cm; $p < 0.01$) and when compared to baseline (5.7 cm; 95% CI: 4.1, 7.3 cm; $p < 0.001$). No associated changes in body weight or body mass index (BMI) were observed.

Changes in systolic blood pressure were primarily observed in people with high blood pressure (> 130 mmHg). For this group of subjects, there was a significant decrease in systolic blood pressure in the placebo treated participants in Group 1 which became insignificant on 4 g seaweed daily (Table 4). In Group 2 subjects, there was a

decrease in systolic blood pressure in the 4 g/d seaweed group which reached significance when the dose increased to 6 g/d ($p < 0.05$).

The iodine content in each 0.5 g capsule ($n = 4$) averaged $38.5 \mu\text{g} \pm 0$.

TSH analysis of archived serum samples revealed no significant changes during any treatment period.

Serum markers of inflammation (nitric oxide and C-reactive protein) and all other serum analytes did not change significantly in either Group 1 or Group 2.

Only minor adverse side effects were noted: soft feces (2 subjects), increased amount of feces (1 subject), transient discomfort of the stomach after taking seaweed (3 subjects), and sense of fullness (1 person). Two subjects reported positive side effects of participating in the study: resolution of pre-existing gastritis (1 subject), and disappearance of chronic headaches (1 subject). Two people complained about taking too many capsules ($n = 2$), and one of these subjects withdrew from the study.

DISCUSSION

Our results indicate that consumption of seaweed (*Undaria*) by a non-seaweed consuming Andean population improves the pathological parameters of MS, namely decreases in waist circumference and blood pressure. It is unlikely that the results seen in our study could be attributed to additional iodine supplementation. Highly effective public health education programs and widespread introduction and use of iodized salt have resulted in almost universal iodine sufficiency in Ecuador. The major health organizations (PAHO, UNICEF, and the International Council for the Control of Iodine Deficiency Diseases [ICCIDD]) have certified Ecuador as free of iodine deficiency disorders.⁴³

Brown seaweeds contain iodine, and the *Undaria* in our study had an average of $77 \mu\text{g/g}$. This provided an additional $308 \mu\text{g}$ of iodine daily for those taking 4 g/d and $462 \mu\text{g}$ daily for those taking 6 g/d. In other studies we have used the same seaweed and subjects have shown no increase in serum TSH concentrations (unpublished data). The results of a clinical trial using a similar brown seaweed (*Alaria esculenta*) which contains $100 \mu\text{g/g}$ of iodine was given at 5 g/d, and found to be associated with only minor transient changes in serum TSH.⁴⁴ The lack of significant changes in TSH during the administration of either 4 g/d or 6 g/d supports the benign nature of the supplement, although only subjects with normal serum TSH values and negative thyroid antibodies should be included in future studies.

Iodine found in brown seaweed is highly variable, and species living side by side in the same shoreline can contain vastly different amounts,⁴⁵ ranging from $16 \mu\text{g/g}$ to several thousand $\mu\text{g/g}$ in the more common kelps. In Japan, where seaweed intake has been estimated at 12 g/d, an amount that includes both dried and fresh seaweed, the very high iodine seaweeds are often soaked in water and cooked before consumption.⁴⁶ Therefore much of the iodine is released. Seaweed supplements, however, are entirely different, and there is no loss of iodine in preparation of the supplements. Thus determining the iodine content of any seaweed used to produce a dietary supplement is important.

A recent study in Korea concluded that dietary seaweed consumption was a significant risk factor for developing MS, however grilled laver, the type of seaweed most commonly consumed by the subjects in the study, was a red seaweed (genus *Porphyra*), not a brown seaweed,⁴⁷ and hence would not contain the carotenoid fucoxanthin, sulfated polysaccharide fucoidan, alginic acid, or phlorotannins, all of which are specific to brown seaweeds. In addition, the study was conducted in male subjects, and used the aggregate diagnosis of MS, rather than specific aspects of the syndrome for comparison. Hence is difficult to compare the two studies beyond providing insight into the specific types of seaweed that may be helpful in decreasing MS.

Interestingly, Japanese women have much lower rates of MS (14.3% in women, 25% in men).⁴⁸ A diagnosis of MS requires central adiposity. Decreased waist circumference but no change in body weight was observed in women in Group 2. The impact of consuming 1.5 tablespoons of seaweed powder (6 g) in the form of 12 capsules daily (6 in the morning and 6 in the evening) would be unlikely to affect overall food intake. This was confirmed by the lack of weight change.

As the major change we observed was in decreased waist circumference among the female subjects treated with the higher dose of seaweed, these changes may be modulated by estrogen metabolism. *In vivo* studies of female mice report sensitivity to the effects of seaweed specific compounds, namely fucoxanthin, the primary brown seaweed carotenoid.²⁹ The proposed mechanism involves upregulation of the uncoupling protein (UCP1) in the mitochondria of adipose tissue, leading to chemical release of energy as heat, rather than storage as fat. Similar to the women in our study, the female mice had decreased visceral fat weight but no change in body weight.

In a separate line of inquiry, fucoidan, the sulfated polysaccharide found almost exclusively in brown seaweeds, was associated with decreased adipose cell differentiation and decreased gene expression (aP2, ACC, and PPAR γ) associated with fat storage.⁴⁹ Although the seaweed treatment provided small amounts of both fucoxanthin (2 mg/g)⁵⁰ and fucoidan (80 mg/g),⁵¹ in Japan, life-long daily exposure to seaweed in Japanese cuisine may have significant protective effects, especially for women.

We also found significant decrease in systolic blood pressure for subjects with high blood pressure at baseline. The decrease in systolic blood pressure with 6 g/d treatment indicates that 6 g/d may be the threshold for an effect on blood pressure. Krotkiewski investigated the effect of seaweed on mild hypertension in a Swedish clinical trial and found 12 g/d to be the minimal effective dose.²⁷ In that study, salt-sensitive individuals experienced twice the benefits reported by salt-insensitive subjects. We did not control for salt sensitivity in our study, and this may be an important variable.

Seaweed may be a CVD "tonic" to improve health, affecting only subjects with elevated systolic blood pressure. Using the meta-analysis estimates based on population CVD rates,⁸ a 2 mmHg reduction was associated with a 7% lower CVD mortality risk. Possible mechanisms that result in the blood pressure lowering effect of seaweed include: the fact that *Undaria*-specific phlorotannins and

isolated dipeptides have similar activity as the angiotensin-converting enzyme (ACE) inhibitor Captopril.⁹ In addition, seaweed has been reported to lower serum sodium levels by preferentially binding to sodium in the gastrointestinal tract. Lower sodium intake/absorption is important in lowering blood pressure for salt sensitive individuals.⁵² The brown seaweed specific cell wall component, alginic acid, has been reported to be critical in both clinical and *in vivo* studies in lowering blood pressure by binding to sodium,^{21,53} as well as having an absorbed component that acts as a calcium channel blocker.⁵⁴

Epidemiologic evidence from Japan demonstrates CVD mortality rates that are 30% lower than in the US. Although daily consumption of seaweed is but one of many dietary and lifestyle differences between residents of these two countries, its contribution to health has generally been overlooked as a potentially important part in terms of nutritional differences between the two countries.

Most of the subjects were educated and had middle class incomes. Few took medications for their diagnosed medical conditions, and articles in the popular press regularly emphasized exercise and dietary changes as important for health. It is likely that the subjects in our study remembered to make these changes when they received the MS diagnosis upon being declared eligible for our study.

A major limitation of the study was the small sample size. A larger study is planned for the future. A second limitation was the study design. We wanted to combine a placebo-controlled trial with a dose escalation trial, and the combination raised questions about the placebo effect in this population. Future studies should include at least a one month run-in period to decrease this problem and questionnaires that capture behavioral and dietary changes. Although we did not assess whether the participant's diet changed during or as a result of their participation in the study, it could be assumed that the changes were minor, since average weights of the participants were stable during the study. Changes in exercise habits might also be important, and should be included in future studies. Large crossover studies, including a placebo run-in period, will be helpful to more accurately determine the effects of seaweed.

Six grams per day dietary brown seaweed consumed by non-seaweed consuming subjects in Ecuador was associated with reductions in two of the main criteria used to define MS, namely reduction in systolic blood pressure for participants with high blood pressure and reduction in waist circumference in women. These results provide insight into how lifelong daily consumption of seaweed by people in Japan may be related to their lower rates of MS. Our study also suggests that brown seaweed supplements may be helpful in reversing some of the symptoms of MS in non-seaweed consuming populations.

AUTHOR DISCLOSURES

No outside funding source was used to support this research. JT provided the funding for the cost of the supplies and donated her time to design the study and analyze the data and prepare them for publication; MB provided input into the design of the study and donated his time to do the study in Quito, Ecuador and ana-

lyze the blood samples; DC donated his time to assist with study design, study implementation and data analysis/interpretation; AS donated his time to interpret the results; LEB donated his time to assist in the data analysis/interpretation of the TSH analyses. Seaweed and funding for the TSH analyses were generously donated by Soriano SA.

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Original Article

Could dietary seaweed reverse the metabolic syndrome?

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食用海藻是否可以逆轉代謝症候群?

除了一些常吃海藻的亞洲國家外，代謝症候群的發生率在世界各地逐步增加。13名有一項代謝症候群症狀的男性(平均年齡 47.4± 9.9 歲)及 14 名女性(平均年齡 45.6± 12.2 歲)納入 Quito Ecuador 隨機雙盲安慰劑試驗。研究對象被分派為第 1 組(1 個月安慰劑，之後為 1 個月 4 克/天海藻[*Undaria pinnatifida*])或是第 2 組(4 克/天海藻 1 個月，之後為 1 個月 6 克/天海藻)。每個月測量血壓、體重、腰圍、發炎生化指標及血脂。統計分析方法為重複測量變異數分析繼之 Tukey's 多重比較。第二組的在吃了一個月 6 克/天海藻之後，收縮壓降低 10.5mmHg(95% CI: 4.1, 16.8 mmHg; $p < 0.05$)，主要是在那些一開始即有較高血壓的人身上。腰圍的改變僅發生在女性，第一組在使用安慰劑一個月之後，腰圍減少 2.4 公分(95% CI: 1.0, 3.7 公分; $p < 0.01$)。第二組女性在使用 4 克/天後，減少了 2.1 公分(95% CI: 0.4, 3.7 公分; $p < 0.05$)，使用 6 克/天一個月後，進一步減了 1.8 公分 (95% CI: 0.1, 3.4 公分; $p < 0.05$)。此外，沒有其他變化。每日食用 4 到 6 克的海藻，是大部分日本人的典型，可能與日本有較低的代謝症候群盛行率有關。

關鍵字：海藻、代謝症候群、高血壓、腰圍、碘、臨床試驗