Clin Nutr Res. 2020 Apr;9(2):90-96
https://doi.org/10.7762/cnr.2020.9.2.90
pISSN 2287-3732·eISSN 2287-3740

cnr
CLINICAL NUTRITION RESEARCH

Original Article

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Short Term Intake of *Undaria pinnatifida* Does Not Affect Bone Biomarkers in Young Korean Women with Low Calcium Intake

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OPEN ACCESS

Received: Mar 30, 2020
Revised: Apr 13, 2020
Accepted: Apr 16, 2020

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Trial Registration
Clinical Research Information Service Identifier: KCT0003307

ABSTRACT

Calcium intake is essential for bone health, but young Korean women have low calcium intakes. Seaweeds have high calcium content, which may affect calcium metabolism. Twenty nine females aged 18–39 years with low calcium intake (< 400 mg/day) participated in a 19-day open-label randomized controlled trial. During the first five days, participants adhered to a controlled-feeding protocol followed by a two-week supplementation period in free-living conditions. The treatment group (n = 14) received an additional 200 mg Ca/day through *Undaria pinnatifida* and *Porphyra* in meals during the controlled-feeding period, and as *U. pinnatifida* noodles during days 6–19. Mineral intake (Ca, P, Mg, Na, and K) was assessed from diet composites and three 24-hour recalls during the controlled-feeding and free-living periods, respectively. Fasting serum levels of calcium, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D (1,25[OH]D), phosphorus, parathyroid hormone (PTH), and alkaline phosphatase (ALP) were assessed at baseline, day 6, and day 19. Statistical analyses were performed by Student's *t*-test and mixed ANOVA. Mean intakes of all minerals during days 1–5 and mean Ca and Mg intakes during days 6–19 were greater in the treatment group compared to the control group. No group effect or group and time interaction was observed in serum biomarkers. Serum 1,25(OH)D increased while PTH and ALP tended to decrease on day 6 but returned to baseline values on day 20. Short-term intake of *U. pinnatifida* and *Porphyra* does not affect calcium metabolism in young Korean women with low calcium intakes.

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Keywords: Seaweed; Calcium; Vitamin D; Biomarkers; Koreans

INTRODUCTION

Adequate calcium and vitamin D intake is essential for the growth and maintenance of bone and the prevention of fractures [1]. Inadequate calcium intake increases bone resorption, which may result in lower bone mineral density (BMD) and fracture risk during later years of life. Females are more prone to fracture as rapid bone loss occurs with menopause [2]. Various medications for postmenopausal women may increase BMD, but all have serious potential side effects and discontinuation results in rapid bone loss yielding BMD similar

Funding

This research was a part of the project titled 'The base study to discover and to commercialize for the resources of sea healing to activate marine industry', funded by the Ministry of Oceans and Fisheries, Korea (20170242).

Conflict of Interest

The authors declare that they have no competing interests.

to prior treatment [3]. However, young Korean females consume approximately half of the Recommended Nutrient Intakes (RNIs) and vitamin D status is the lowest in this age-group among the Korean population [4,5]. Therefore, strategies to maximize and maintain bone mass, including adequate calcium and vitamin D intake and weight-bearing exercise, are necessary to prevent fracture.

Foods high in calcium content are few in Korea. Consumption of milk and dairy products is lower in Asia than Western countries as it is not part of the traditional diet and many conceive oneself to be lactose intolerant [6]. Foods of the traditional Korean diet with high calcium content include anchovies, whitebait, and seaweed [7]. Seaweed is frequently consumed as side dishes and soup. However, due to the high fiber content of seaweed, it is unknown whether the calcium in seaweed is well absorbed and can affect calcium metabolism. Recent studies indicate that some fibers increase calcium absorption in the gut, possibly by influencing the gut microbiome [8-10]. Therefore, we aimed to assess the effect of *Undaria pinnatifida* and *Porphyra*, the two most commonly consumed seaweeds in Korea with high calcium content, on biomarkers of calcium metabolism.

MATERIALS AND METHODS

Subjects

Young females aged 18–39 years were recruited through flyers and internet social media to participate in this 19-day clinical trial (June 25 to July 13, 2018). Inclusion criteria were healthy females with low (< 400 mg/day) Ca intake able and willing to adhere to the controlled diet. Women pregnant, breast-feeding, planning to become pregnant, taking hormones or steroids, having liver, kidney, or thyroid diseases, or having had a fracture during the past 6 months were excluded. Calcium intake was assessed by food frequency questionnaire. The final participants were from Gwangju and Cheollanam, Cheollabuk, Kyounggi, and Gangwon province. Participants were randomized by the research staff the day before the controlled feeding period. Participants were asked to wear sunblock and/or clothing to block ultraviolet exposure during outdoor activities. All protocols were approved by the Chonnam National University Institutional Review Board (1040198-180320-HR-017-04) and registered at the Clinical Research Information Service (https://cris.nih.go.kr: KCT0003307).

Diet

Participants were housed in Chosun University housing facilities in Wando-gun, Cheollanam-do during the controlled feeding period (days 1–5). Diets were planned based on the Dietary Reference Intakes for Koreans (KDRI) or mean intake of Koreans, with the exception of calcium. The target calcium intake of the basal diet was 400 mg/day. All diets were planned and served as 1,500, 1,800, 2,100, or 2,400 kcal/day according to one's caloric needs. The basal diet consisted of common Korean foods such as rice, soup, kimchi, and side dishes. The treatment group was given 20 g (dry weight) of additional seaweeds (18 g *U. pinnatifida* and 2 g *Porphyra*) as side dishes or mixed in soup, sauces, drinks, etc. to provide an additional 200 mg/day of calcium. *U. pinnatifida* and *Porphyra* samples were analyzed for mineral content prior to the study by inductively coupled plasma optical emission spectroscopy (ICP-OES) as detailed below. All food was weighed to 0.1 g prior to serving. Deionized water was provided *ad libitum*. Participants were provided activities during the 5-day controlled feeding period and were supervised in order to verify that they did not consume foods or beverages other than those provided. Duplicate diets were freeze dried and analyzed for mineral content.

https://doi.org/10.7762/cnr.2020.9.2.90

After the controlled feeding period, participants returned to their normal daily routine (days 6–19). Those in the treatment group were provided seaweed noodles (98% *U. pinnatifida*) which were analyzed for mineral content by ICP-OES as detailed below. Each pack contained 316 mg of calcium. Therefore, participants were provided 8 packs of noodles to consume over the remaining 13-day period (days 6–18: 2 packs per every 3 days) to target, on average, an additional 200 mg of calcium intake per day through seaweed (Seaweed PoSlim; Haechungjung, Wando-gun, Korea). Compliance was measured by self-report and the number of packs returned. The control group did not receive any placebo. All participants were asked to continue their normal diet. As part of a program during the controlled feeding period, subjects were provided an education session by dietitians with hands-on training on portion size estimation and how to complete a self-reported 24-hour recall. During the free-living period (days 6–19), research staff requested the subjects to complete three 24-hour recalls on random days (2 weekdays and 1 weekend day) without the subjects' prior knowledge.

Diet analysis

Prior to the controlled feeding study, seaweeds and seaweed noodles were analyzed for mineral content. *U. pinnatifida* was soaked in deionized water for ≥ 10 minutes, drained, dried overnight, powdered, and analyzed for mineral content. *Porphyra* was also dried in an oven overnight before analysis. The seaweed noodles provided were prepared as participants would actually consume the noodles, dried in an oven, and analyzed for mineral content. Freeze dried duplicate diets provided during the controlled-feeding period were also analyzed for mineral content. Minerals analyzed include Ca, P, Mg, Na, and K which were assessed by ICP-OES (Optima 7300 DV; PerkinElmer, Waltham, MA, USA). Food intake during the free-living period was assessed from self-reported 24-hour recalls and analyzed using CAN Pro 5.0 (web version; The Korean Nutrition Society, Seoul, Korea) software. Total mineral intake during the free-living period was calculated as:

$$Mean\ daily\ mineral\ intake = \frac{total\ mineral\ intake\ from\ three\ 24-hour\ recalls\ (CAN-Pro\ analysis)}{3} + \frac{total\ mineral\ intake\ from\ seaweed\ noodles\ (ICP-OES\ analysis)}{13}$$

Biomarker analysis

Fasting serum samples were collected on the morning of days 1, 6, and 19. Serum were centrifuged and assessed for Ca (JW CA; JW Bioscience, Seoul, Korea), P (JW IP; JW Bioscience), intact parathyroid hormone (PTH; chemiluminescence immunoassay, Elecsys PTH; Roche Diagnostics, Risch-Rotkreuz, Switzerland), alkaline phosphatase (ALP; cobas c 111 analyzer, Roche Diagnostics), 25-hydroxy vitamin D_3 (25[OH]D; radioimmunoassay [RIA] by 25OH-VIT.D3-RIA-CT KIP1961; DIAsource ImmunoAssays SA, Nivelles, Belgium), and 1,25-dihydroxyvitamin D (1,25[OH]D; RIA by 1,25(OH)2-VIT.D-RIA-CT KIP1961; DIAsource ImmunoAssays SA).

Statistics

Comparisons of baseline characteristics was performed by Student's t-test. Group differences according to time were assessed by mixed analysis of variance. Post hoc analysis was performed by least square means. Null hypotheses were rejected when $p < 0.05$. SAS 9.4 (SAS Institute Inc, Cary NC, USA) was used for all analyses.

https://doi.org/10.7762/cnr.2020.9.2.90

Table 1. Subject characteristics

Characteristics	Control (n = 15)	Treatment (n = 14)	p value
Age (yr)	20.3 ± 2.2	20.1 ± 1.4	0.78
Height (cm)	160.3 ± 4.5	160.5 ± 5.6	0.90
Weight (kg)	55.4 ± 9.0	58.1 ± 10.6	0.47
BMI (kg/m^2)	21.5 ± 3.1	22.6 ± 3.8	0.44
Calcium intake (mg/day)	264.9 ± 98.8	282.7 ± 76.2	0.59

Values are mean ± standard deviation. Differences between means were determined by Student's t-test.
BMI, body mass index.

RESULTS

Participants

A total of 31 participants were enrolled in the study. One subject assigned to the treatment group dropped out of the study before the first blood draw. Another participant in the control group had a fracture on the morning of the third blood draw (day 19) and thus was not able to complete the study. Therefore, we analyzed the remaining 29 participants. Participants were 20.2 years of age with a mean body mass index (BMI) of 22.0 and low calcium intake (mean 273 mg/day; **Table 1**). No differences were found between the control and treatment group.

Nutrient intake

During the controlled feeding period, mean intakes of Ca, P, Mg, Na, and K were greater in the treatment group compared to the control group (**Table 2**). According to the 24-hour diet recalls, intake of energy and the above minerals from diet did not differ between groups during the free-living period (data not shown). Mean compliance of seaweed noodle intake was 75.9% where 10 of the 14 subjects consumed ≥ 6 of the 8 (≥ 75%) packs of noodles supplied. When seaweed noodle intake was taken into account, the treatment group had higher mean intakes of Ca and Mg (p = 0.02 and p = 0.03, respectively; **Table 2**).

Table 2. Energy and mineral content of menus provided during the controlled feeding trial and 24-hour dietary recall analysis of energy and minerals consumed during the free-living period

Nutrients	Control (n = 15)	Treatment (n = 14)	p value
Controlled feeding*			
Energy (kcal/day)	1,892.0 ± 123.9	1,907.1 ± 133.5	0.75
Ca (mg/day)	289.7 ± 6.0	440.3 ± 13.5	< 0.0001
P (mg/day)	1,364.6 ± 47.2	1,433.1 ± 69.0	0.004
Mg (mg/day)	209.8 ± 5.0	316.2 ± 8.1	< 0.0001
Na (mg/day)	2,545.7 ± 54.1	3,111.7 ± 116.3	< 0.0001
K (mg/day)	2,039.7 ± 62.7	2,184.6 ± 72.3	< 0.0001
Free-living†			
Energy (kcal/day)	1,578.7 ± 549.3	1,738.0 ± 1,017.0	0.61
Ca (mg/day)	359.8 ± 195.1	541.3 ± 186.3	0.02
P (mg/day)	774.6 ± 319.2	985.1 ± 491.7	0.19
Mg (mg/day)	82.9 ± 62.4	156.9 ± 105.3	0.03
Na (mg/day)	2,772.2 ± 1,589.7	3,292.2 ± 1,281.0	0.35
K (mg/day)	1,676.8 ± 805.7	2,209.6 ± 922.1	0.12

Values are mean ± standard deviation. Comparisons between groups were made by t-test.
ICP-OES, inductively coupled plasma optical emission spectroscopy.
*Energy content was assessed by analyzing the recipes and actual intake with CAN Pro 5.0 software. Mineral content was assessed by ICP-OES of freeze dried diet composites. †One subject in the control group is missing data. Energy and nutrient intakes were assessed from three 24-hour diet recalls analyzed with CAN Pro 5.0 software for the control group. Self-reported compliance and actual ICP-OES data of the seaweed noodles was added to the CAN Pro analyses for the treatment group.

https://doi.org/10.7762/cnr.2020.9.2.90

Table 3. Changes in serum biochemical markers

Variables	Control (n = 15)			Treatment (n = 14)			Group	Time	Group*time
	Baseline	Day 6	Day 19	Baseline	Day 6	Day 19			
Serum calcium (mg/dL)	9.21 ± 0.20^{a}	9.36 ± 0.27^{bc}	9.43 ± 0.23^{c}	9.24 ± 0.30^{ab}	9.35 ± 0.27^{abc}	9.45 ± 0.25^{cd}	0.87	0.0006	0.93
Serum 25(OH)D (ng/mL)	15.51 ± 4.25^{a}	15.20 ± 5.80^{a}	23.03 ± 9.00^{b}	16.83 ± 6.72^{a}	16.37 ± 6.27^{a}	20.18 ± 5.45^{ab}	0.94	< 0.0001	0.14
Serum 1,25(OH)D (pg/mL)	37.47 ± 7.23^{a}	47.12 ± 9.10^{b}	38.94 ± 8.99^{ac}	38.63 ± 11.23^{a}	45.32 ± 10.77^{bc}	40.16 ± 11.52^{ab}	0.94	0.001	0.72
Serum phosphorus (mg/dL)	3.84 ± 0.51^{a}	4.23 ± 0.51^{b}	4.19 ± 0.52^{bc}	3.86 ± 0.54^{ac}	3.99 ± 0.41^{ab}	3.97 ± 0.63^{ab}	0.32	0.03	0.37
Serum intact PTH (pg/mL)	38.4 ± 10.5^{a}	37.8 ± 8.4^{b}	39.7 ± 18.3^{ac}	41.6 ± 10.2^{a}	29.8 ± 9.9^{bc}	45.7 ± 15.5^{a}	0.30	< 0.0001	0.77
ALP (U/L)	58.6 ± 11.1	55.1 ± 13.1	56.2 ± 14.3	57.1 ± 15.3	52.3 ± 14.1	52.7 ± 16.0	0.58	0.01	0.77

Values are mean ± standard deviation. Mixed analysis of variance was used to determine the group and time effects. Means within a row without the same alphabet differ.
PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D_3, 1,25(OH)D, 1,25-dihydroxyvitamin D; ALP, alkaline phosphatase.

Serum biomarkers

All baseline serum measures were within normal range with the exception of 25(OH)D. Mean serum 25(OH)D was below the target status for individuals recommended by the Institute of Medicine (currently the National Academy of Medicine) and KDRI (> 20 ng/mL). No differences in biomarker status between groups were found at baseline (**Table 3**). Serum Ca increased with time, but was within normal range. On the other hand, mean serum 25(OH)D increased with time to reach above 20 ng/mL by day 19. Serum 1,25(OH)D and P levels increased while PTH level decreased during the controlled feeding period, regardless of treatment, but returned to baseline values by day 19. No group effect was detected for ALP, but a time effect was found where ALP tended to decrease after the controlled-feeding period and then return to baseline levels by day 19.

DISCUSSION

Additional calcium intake of 200 mg through seaweed, primarily *U. pinnatifida,* in young Korean females did not affect calcium metabolism. In addition, changes in serum biochemical markers were prevalent during the controlled-feeding period, indicating that a balanced diet itself or other environmental factors may have affected the outcomes.

Previous studies on the effect of seaweed on bone are few. Researchers found that *Hijikia fusiforme* extract increased proliferation, collagen content and mineralization, but not ALP activity, of MCT3T3-E1 cells [11]. Similarly, growing Sprague Dawley rats fed 0.5%–1.5% *Kjellemaniella crassifolia* (also called sea tangle), had higher bone breaking strength and ash content of the femur [12]. However, femur length and serum biomarkers were not affected by *Kjellemaniella crassifolia* intake. We are the first to investigate the effect of *U. pinnatifida* and *Porphyra* on calcium metabolism. From our short-term study using biochemical markers, the calcium in *U. pinnatifida* and *Porphyra* does not seem to affect calcium metabolism. Based on our results, the high fiber content in seaweeds may interfere with the absorption of calcium in these foods. On the other hand, some fibers have been reported to increase calcium absorption and retention [8-10]. Though the mechanism is not clear, it is thought that these fibers increase calcium absorption in the gut through changes in the microbiome [9,10]. Another explanation may be that the greater sodium intake from seaweed consumption increased calcium excretion, especially during the controlled-feeding period. In addition to increased calcium intake with seaweed consumption, *U. pinnatifida* has been reported to have estrogen-like activities in breast cancer cells [13]. However, high fiber intake is inversely associated with sex-hormones and positively associated with risk of anovulation in young women in the US [14]. Sex-hormones directly affect bone metabolism, but the effect of *U.*

https://doi.org/10.7762/cnr.2020.9.2.90

pinnatifida and *Porphyra* intake on sex-hormones were not investigated in this study. As no change was identified in the biomarkers we analyzed, it is unlikely that sex-hormones in our healthy population were affected. Regardless, this is the first study to investigate the effect of *U. pinnatifida* intake on calcium metabolism in humans.

Due to the short duration of the study, we were unable to assess long term effects of seaweed on bone. In order to eliminate controllable variations during the study, we introduced a 5-day controlled feeding setting, where all participants were housed and provided the same activities and meals. The changes in serum biomarkers from baseline seem to have come from the controlled setting, rather than intake of seaweed. In addition, owing to the 2-week free-living period, more variation due to participants' life-style may have been introduced. The 20-day trial is too short to observe drastic changes in bone metabolism as change in bone mineral density is slow and difficult to detect in relatively healthy young adults. Therefore, the use of intermediate measures, such as biomarkers, calcium absorption, and calcium retention, are more practical measures for clinical trials. The biomarkers used in our study, serum 1,25(OH)D, PTH, and ALP, are indirect measures of calcium metabolism and have high inter- and intra- individual variation. More sensitive measures such as calcium balance must be performed to accurately assess the effect of seaweed on calcium retention.

Rather than seaweed itself, the provided balanced diet and sun exposure during the clinical trial may have affected the biomarkers investigated. Regardless of group, PTH decreased while 1,25(OH)D and serum phosphorus increased during the controlled feeding period. These markers tended to return to baseline values at day 19. In the endocrine system, low serum Ca increases PTH, followed by the activation of 25(OH)D to 1,25(OH)D by PTH and thus the direction of change in these hormones are identical [15]. However, the direction of change in biomarker concentration in our subjects differs from the previously reported mechanism. Serum 1,25(OH)D changes within 3–4 hours, and thus some unknown immediate factor may have led to the increase in 1,25(OH)D on day 6, which was followed by the increase in serum calcium, despite of being within normal range, and a decrease in PTH through its negative feedback loop. In addition, the decrease in PTH may result in increased serum phosphorus as renal phosphate reabsorption is increased. However, we are unable to identify the specific cause of increase in 1,25(OH)D. The increase in serum 25(OH)D level by day 19 may be due to sun exposure during the stay on the island despite of efforts to block UV ray exposure, as the half-life of serum 25(OH)D is approximately 3–4 weeks. The change in serum 25(OH)D level appeared later during the trial and serum 25(OH)D is known does not correlate with 1,25(OH)D and thus is unlikely to have affected other bone biomarkers within 5 days [15]. Further investigations with a city control group that did not participate in the controlled feeding or travel to the island may help understand the change in serum metabolites.

CONCLUSION

Intake of *U. pinnatifida* and *Porphyra* does not affect bone biomarkers in healthy young Korean females with relatively low calcium intake. Further studies are required to elucidate the causes of change in serum biomarkers observed in the participants during the controlled feeding period of the study.

https://doi.org/10.7762/cnr.2020.9.2.90

ACKNOWLEDGEMENTS

The authors would like to thank Mr. Yongwan Kim at the Center for Research Facilities at the Chonnam National University, for extending support to analyze the diet samples by ICP-OES, Ms. Bo-eun Jun at the Wando County Health Center and Hospital for performing the blood draws, and Ms. Lee Cho-hee and Mr. Lim Dae-yong at the Wando County office for facilitating the arrangements for local accommodation and tours.

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