

〈Regular Article〉

Effects of freeze-dried tofu (Koya-dofu) therapy on migraine : A second report

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ABSTRACT Background: Migraines in women, particularly those associated with menstruation, are often resistant to treatment. In 2008, Kim *et al.* reported that freeze-dried tofu (Koya-dofu) therapy improved both migraine symptoms and menopause-related complaints in women. Koya-dofu primarily contains soybean isoflavones, which exhibit phytoestrogenic activity. This study investigates whether daily intake of freeze-dried tofu, rich in soy isoflavones, is effective in alleviating migraines in women.

Methods: Ten female patients attending the internal medicine outpatient clinic of our hospital were enrolled in this study. Each patient consumed approximately 50 g (dry weight) of commercially available freeze-dried tofu (Koya-dofu) daily for one month. Headache frequency and severity were evaluated using patient-maintained headache diaries. Blood estradiol (E2) levels were measured before and after the therapy.

Results: Among the six patients assessed over a four-week interval, three reported a reduction in the number of headache days. Two of four patients showed improvement over a two-week interval. Regarding headache severity, four of six patients experienced improvement over four weeks, and one of four over two weeks. Additionally, eight out of ten patients exhibited stable or decreased blood E2 levels following the therapy.

Conclusions: Freeze-dried tofu (Koya-dofu) therapy was associated with symptom improvement in a number of cases. These findings suggest it may be a beneficial adjunctive treatment option for women suffering from migraines.

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Key words : Migraine, Freeze-dried tofu therapy, Phytoestrogen, Soybean isoflavone

INTRODUCTION

Migraines in women, particularly those related to menstruation, are often resistant to standard

treatments. In 2008, Kim *et al.* reported that freeze-dried tofu (Koya-dofu) therapy significantly improved migraine and menopausal symptoms in

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women¹⁾. In a previous study conducted by the author involving four cases, all subjects experienced improvement, as previously reported²⁾.

OBJECTIVE

To evaluate the effectiveness of freeze-dried tofu (Koya-dofu), which contains soy isoflavones with phytoestrogenic effects, in alleviating migraines in women.

SUBJECTS AND METHODS

The study included 10 female outpatients from the internal medicine department of our hospital, ranging in age from 19 to 53 years (mean age: 31.1 years). After obtaining informed consent, participants were instructed to consume approximately 50 g (dry weight) of commercially available freeze-dried tofu (Koya-dofu) daily for one month, following the protocol reported by Kim *et al.* Subjects were allowed to prepare the tofu in any manner they preferred. Participants

recorded their headache symptoms in a headache diary, and changes in headache frequency and severity were assessed by comparing entries from before and after the freeze-dried tofu (Koya-dofu) therapy (hereafter referred to as "therapy"). Blood samples were collected before and after the therapy to measure serum estradiol (E2) levels. This study was approved by the Ethics Committee of Kawasaki Medical School (approval number 878-4).

RESULTS

Of the 10 participants, 6 maintained headache diary records for four weeks before and after therapy, while 4 maintained diaries for two weeks before and after therapy. Among the six patients with four-week diary records, three showed a reduction in the number of headache days after the therapy. Among the four patients with two-week records, two demonstrated improvement. Regarding headache severity, of the six patients evaluated over four weeks, four reported a decrease in headache

Table 1. Changes in the number and severity of headaches before and after 4 weeks of freeze-dried tofu (Koya-dofu) therapy

| Case | Age | Number and severity of headaches (before therapy) | Number and severity of headaches (after therapy) (Improvements are in bold.) | Effects | |
|------|-----|--|---|---------|----------|
| | | | | number | severity |
| 1 | 42 | 14 days (Headache every other day) Often fall asleep. Oral administration of loxoprofen is required. Severity: moderate | 11 days No need to take loxoprofen. Reduced risk of staying in bed. Severity: mild to moderate | ○ | ○ |
| 2 | 19 | 3 days Severity: mild to moderate | 7 days Severity: mild to severe Lack of sleep, etc., and other irregular lifestyle habits. | × | × |
| 3 | 41 | 13 days Severity: mild to severe | 8 days Severity: mild to moderate | ○ | ○ |
| 4 | 21 | 6 days Severity: mild to moderate Zolmitriptan is required. | 5 days Severity: mild No need to take zolmitriptan. | × | ○ |
| 5 | 29 | 14 days Severity: mild to severe Lomerizine combination | 13 days Severity: mild to moderate Lomerizine combination | × | ○ |
| 6 | 53 | 25 days Severity: mild to moderate Lomerizine combination | 14 days Severity: mild to moderate No need to take lomerizine. | ○ | × |

Table 2. Changes in the number and severity of headaches before and after 2 weeks of freeze-dried tofu (Koya-dofu) therapy

| Case | Age | Number and severity of headaches (before therapy) | Number and severity of headaches (after therapy) (Improvements are in bold.) | Effects | |
|------|-----|---|---|---------|----------|
| | | | | number | severity |
| 7 | 23 | 14 days (Headache every day) Vomiting once. Severity:mild to severe | 5 days Severity:mild | ○ | ○ |
| 8 | 22 | 6 days Severity:mild to moderate | 2 days Severity:mild to moderate | ○ | × |
| 9 | 40 | 4 days Severity:mild to severe Menstrual pain | 5 day Severity:mild to severe Menstrual pain disappears. Significant reduction in non-menstrual headaches. | × | × |
| 10 | 21 | 6 days Severity:mild to moderate | 6 days Severity:mild to moderate | × | × |

Table 3. Changes in serum estradiol (E2) levels before and after freeze-dried tofu (Koya-dofu) therapy

| Case | before therapy (pg/ml) | after therapy (pg/ml) |
|------|------------------------|-----------------------|
| 1 | 188 | 14 |
| 2 | 31 | 27 |
| 3 | 157 | 31 |
| 4 | 110 | 42.5 |
| 5 | < 5 | 9.6 |
| 6 | < 5 | < 5 |
| 7 | 28 | 23 |
| 8 | 188 | 145 |
| 9 | 170 | 46 |
| 10 | 39 | 41 |

severity. Among those with two-week records, one patient showed improvement (Tables 1 and 2).

Serum E2 concentrations remained unchanged or decreased in 8 out of 10 patients following the therapy (Table 3).

Case presentation - Case 6

A 53-year-old woman (case 6) exhibited a marked therapeutic response. She had a long history of headaches, experiencing attacks three to four times per week. Her headaches were pulsatile, left-sided, and accompanied by nausea, but without aura. She regularly used loxoprofen, which provided relief; however, both the frequency and intensity of her headaches worsened approximately six weeks before her initial hospital visit. Oral sumatriptan

was prescribed but proved ineffective. She reported prior success with zolmitriptan. A head computed tomography scan revealed no abnormalities. Her baseline serum E2 level was below 5.0 pg/ml. She was prescribed lomerizine hydrochloride and zolmitriptan, but no clinical improvement was observed, leading to the discontinuation of lomerizine hydrochloride. Acetaminophen was subsequently prescribed on an as-needed basis. Before initiating therapy, she experienced headaches on 25 out of 28 days, with mild to moderate severity. After starting the freeze-dried tofu therapy, the number of headache days decreased significantly to 14 out of 28 days, with similar severity. She took acetaminophen only three times during this period, and zolmitriptan was not required. Her serum E2 level remained below 5.0 pg/ml after therapy.

The patient incorporated the freeze-dried tofu into a variety of dishes, including sweet and spicy pork wraps, deep-fried tofu, egg-bound tofu, crispy tofu sticks, stir-fried pork with egg, sauce-style pork cutlets, minced chicken soup dumplings, hamburger steak, miso soup with nameko mushrooms and komatsuna, thickened shiitake mushrooms, keema curry, deep-fried spring rolls, pork wrapped in shiso leaves, deep-fried eggplant with tofu, deep-fried ham cutlet sandwiches, mixed tofu sandwiches, and

mapo-style tofu. The patient commented, "I was able to enjoy the variety of menus for a month of treatment. I've had fewer headaches and feel better."

DISCUSSION

Freeze-dried tofu (Koya-dofu) is a traditional Japanese food, and one of its primary components is soy isoflavones. Isoflavones are glycosides predominantly derived from legumes, particularly soybeans. Compounds such as genistein and daidzein are known as phytoestrogens due to their structural similarity to estrogen and their estrogen-like biological activity³⁾. Numerous studies have reported that soy isoflavones are effective in alleviating various menopausal symptoms in women⁴⁻⁶⁾. The prevalence of migraines in women is approximately 3.6 times higher than in men, with the highest incidence observed in women in their 20s to 40s. Notably, the prevalence of migraine does not differ between sexes until puberty, suggesting a strong correlation between female hormonal activity and migraine pathophysiology⁷⁾. In this study, freeze-dried tofu (Koya-dofu) therapy led to improvements in headache frequency and/or severity in a significant number of participants, indicating its potential as an option for managing migraines in women.

Regarding the observation that serum E2 levels remained unchanged or decreased in 8 out of 10 subjects, several factors may account for this finding. First, blood samples were not consistently collected immediately following the completion of therapy. Second, as E2 levels naturally fluctuate with the menstrual cycle (which typically ranges from 25 to 38 days), the timing of blood collection was not standardized according to each individual's cycle, potentially impacting the accuracy of hormone level comparisons.

Two primary factors are believed to contribute to cases in which therapy was ineffective: 1. Lifestyle factors: In some cases, worsening of headache

frequency or severity may have been influenced by poor lifestyle habits, such as inadequate sleep. 2. Equol Production Variability: Soy isoflavones have a similar effect to female hormones because their structure is similar to estrogen, and are known to be effective in alleviating menopausal symptoms and maintaining bone density. Soy isoflavones (particularly daidzein) are metabolized in the intestine. While some individuals absorb daidzein directly, others convert into equol, a metabolite with significantly higher estrogenic activity. This conversion depends on the presence of specific gut microbiota known as "equol-producing bacteria." To date, around ten types of these bacteria have been identified, although additional strains may exist. Studies suggest that approximately 50% of Japanese individuals and 20-30% of Westerners possess equal-producing gut flora⁸⁾. Therefore, it is possible that some of the non-responsive cases involved participants who lacked these bacteria and were consequently unable to benefit fully from the phytoestrogenic effects of soy isoflavones.

CONCLUSIONS

This study evaluates the effects of freeze-dried tofu (Koya-dofu) therapy on migraines in women. Improvements in headache frequency and/or severity were observed in several cases, suggesting that this dietary intervention may be a viable adjunctive treatment option for women suffering from migraines.

The abstract of this study was presented at the 49th Annual Meeting of the Japanese Headache Society (November 19, 2021, Shizuoka City).

CONFLICT OF INTEREST

The author has no conflict of interest to declare.

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