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SHORT COMMUNICATION

Correlations between "hie-sho" interview score and progesterone, fat intake, and Kupperman index in pre- and post-menopausal women: a pilot study

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Abstract
Japanese menopausal women who feel cold, even in a warm room, are said to be experiencing "hie-sho." We assessed the magnitude of coldness by a "hie-sho" interview score. The association between the magnitude of coldness and female hormones, fat intake, and menopausal symptoms is unknown. The aim of the present study was to elucidate the relationship between the hie-sho interview scores and female hormones, fat intake, Kupperman index in pre- (pre group) and post- (post group) menopausal women. The hie-sho interview scores, Kupperman index questionnaire results, dietary survey to analyze fat intake, and body weight were analyzed, and plasma estradiol, progesterone, and lipid levels were measured in the subjects in the pre ($n=9$) and post ($n=11$) groups. Plasma female hormones and fat intake were different, but the total Kupperman index was not different between pre and post groups. Plasma progesterone was positively correlated with the hie-sho score only in the post group. Plasma triglyceride was positively correlated with the hie-sho score only in the pre group. Intake of cholesterol, arachidonic acid, and docosapentaenoic acid was negatively correlated with the hie-sho score only in the pre group. The positive correlation between total Kupperman index and hie-sho score was observed only in the pre group. These results indicated that progesterone level was related to coldness in post-menopausal women. Fat intake, plasma triglyceride, and menopausal symptoms may be related to coldness in pre-menopausal women.

Keywords Cold constitution · Chilliness · Hie-sho · Coldness · Kupperman index

Introduction

Some Japanese women experience a coldness sensation, even in a warm room (23–26 °C) where most people feel thermally comfortable [1], called "hie-sho." Takatori surveyed middle-aged Japanese women in an outpatient department of a hospital (survey respondents: $n=98$; average age: 41 years), and found 66 who had experienced hie-sho [2]. These results indicate that many middle-aged Japanese women experience this coldness sensation. It has not been revealed whether hie-sho is a specifically Japanese symptom. In Switzerland, there is a symptom called "cold extremities" like hie-sho; however, even in Japan the diagnosis criteria of hie-sho are not standardized, and several scales have been reported in previous studies [2–4]. In one study using a scale, plasma thyroid hormone and skin surface temperature of the fingertip in young women with hie-sho were lower than that in young women without hie-sho at an ambient temperature of 23.5 °C [3]. In another study using a different scale that explored subjective coldness in any parts of the body [5], the systolic and diastolic blood pressures and heart rate were lower in young women with hie-sho than in young women without hie-sho at an ambient temperature of 25 °C [6, 7]. It can be deduced that young women with hie-sho may have problems with secretion of thyroid hormone and regulation of blood circulation. On the other hand, the characteristics of hie-sho in middle-aged women are as yet unknown.

It was reported that 70% of women and 50% of men in an outpatient department of a hospital experienced hie-sho [8], suggesting that hie-sho may be common in women but not in

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men in Japan. Therefore, it is speculated that progesterone and estradiol levels may be related to hie-sho; however, the effect of female hormones on hie-sho in women has not been evaluated. Plasma estradiol and progesterone levels become lower after menopause. We divided the middle-aged women subjects into two groups: pre- and post-menopausal women, and compared the hie-sho scores between groups.

BMI, body weight [5–7, 9], and body fat percentage [6, 7, 9] were lower in young women with hie-sho than young women without hie-sho, suggesting that low body fat may be a characteristic of hie-sho. The young Japanese women that answered a hie-sho questionnaire about favorite foods (respondents: $n = 301$) did not like meat, fish, seafood, or egg, compared to women without hie-sho (survey respondents: $n = 222$) [10]. These foods contain fats such as cholesterol, triglycerides, arachidonic acid, and docosapentaenoic acid. Therefore, it can be suggested that fat intake may be related to hie-sho. A previous study that used Cornell medical index scores to evaluate subjective mental and physical symptoms [11] found that somatic complaints in women with hie-sho were greater than those in women without hie-sho. This Japanese questionnaire (survey respondents: $n = 318$) [12] indicated that somatic complaints may be related to hiesho. Thus, the present study aimed to investigate the correlation between fat intake (determined by a diet survey), Kupperman index (that evaluated symptoms during the menopause [13]), and hie-sho score in pre- and post-menopausal women.

To elucidate the relationship between hie-sho score and female hormones, fat intake, and symptoms during menopause, we examined hie-sho score, plasma estradiol and progesterone concentrations, fat intake in diet, and Kupperman index in pre- and post-menopausal women in a pilot study.

Participants and methods

Subjects

We recruited the subjects by handing out fliers at Nara Women's University. Nine pre-menopausal women (age 47.1 ± 0.9 years; pre-menopausal group) and eleven post-menopausal women (age 52.5 ± 0.3 years; post-menopausal group) participated in the present study. The following women were excluded from the study: (1) those whose menstrual cycle during the last 3 months appeared to be within 18 days or over 45 days (excluded from the pre-menopausal group); (2) those whose period of amenorrhea was under 12 months (excluded from the post-menopausal group); (3) those whose BMI was under 18.5 kg/m^2 or over 30 kg/m^2; (4) those who had had ovariectomy surgery; (5) those who were ill on the day of the experiment; (6) those who took medicines and supplements; (7) those who were smokers. We excluded the women who took medicines and supplements because it might affect the answers in the hie-sho interview. All the subjects provided informed consent for the experimental protocol, which was approved by the Human Investigation Committee of Nara Women's University.

Experimental protocols

The experiment was performed in a room with an ambient temperature of 25 °C to avoid seasonal effects. In the pre-menopausal group, the menstrual cycles during last 4 months were investigated. The experiment day was set during the menstrual phase after the start of menstruation in the pre-menopausal group subjects. The subjects were not allowed to eat stimulating, oily, or salty foods, or alcohol after 21:00 on the evening before the day of the experiment. The stimulating foods included tea, coffee, and hot foods. The subjects were asked to survey their diets for 2 consecutive or non-consecutive days (if they had previous plans) after the experiment day to examine fat intake. The number of days for the diet survey were based on a pre-experiment in our laboratory to investigate the effect of four menstrual cycle phases on fat intake in young women. The jobs of subjects were not asked in the present study; thus, it was unknown whether the days of diet survey were work days or holidays. On the day of the experiment, the subjects drank water (150 ml) to avoid dehydration before the experiment, and rested in a seated position. They underwent a 10-question hie-sho interview [3] and an interview to determine the Kupperman index. Body weight and percent of fat were measured (Karada Scan, OMRON HEALTHCARE Co., Ltd., Japan). Thermal perceptions were not assessed, because we did not perform thermal stimulation in the present study. A medical doctor collected blood samples (10 ml) from the subjects.

Measurements

10-Question hie-sho interview

The 10-question hie-sho interview reported by Nagashima et al. [3] was used. The items are shown in Table 1. The answers to all questions were yes or no. There were 10 questions about coldness of body, and subjects who scored more than seven were defined as experiencing hie-sho. We used this scale because it has been used in previous studies [3, 14, 15]. In addition, the interview specializes in hie-sho, rather than the Cornell medical index that evaluates subjective mental and physical symptoms [11]. The interview contained typical complaints of those suffering from unusual coldness [3]. Thus, we thought that the number of items checked in the hie-sho interview questionnaire reflected the magnitude of complaints of daily unusual coldness. The total score of the interview was averaged in each group as previously reported [15].

Table 1 10-Question hie-sho interview. This table was modified from a previous study [3]. Cited from Nagashima et al. [3]

Do you or are you
1. Sensitive to a reduction in environmental temperature?
2. Feel colder in a cold environment than others do?
3. Sometimes feel cold even in summer?
4. Dislike being barefoot even in summer due to coldness?
5. Feel cold in an air-conditioned room in summer when most people feel comfortable?
6. Need thicker clothes than others do?
7. Need an electric blanket for better sleep in winter?
8. Wear socks while sleeping in winter?
9. Often wake up due to coldness or cold extremities in winter?
10. Often have pain or color changes in the fingertips or toes due to bad circulation in cold?

Blood sampling

The mixed blood and heparin were centrifuged (3000 rpm for 20 min at 4 °C), and the plasma was stored at − 80 °C until the assay was performed. The plasma levels of estradiol, progesterone (chemiluminescent immunoassay method), triglyceride (enzyme method), and HDL- and LDL-cholesterol (direct method) were determined at SRL, Inc. (Tokyo, Japan).

Diet survey

We instructed the subjects to eat foods as usual. The subjects noted down the contents of meals for the survey, and sent pictures of meals and the nutritional information of commercial items to the experimenters. The amounts of nutrients in the hand-made meals were measured by a scale (Mini scale MS-2000, CUSTOM corporation, Tokyo, Japan) and were noted for the survey. The amounts of nutrients in the prepared foods and general intake were noted by the subjects for the survey depending upon their knowledge. After the diet survey, the lipid components were calculated using software (Excel Eiyokun®, KENPAKUSHA, Tokyo, Japan).

Kupperman index

The Kupperman index was developed to quantify indefinite symptoms during the menopause [13]. Alder criticized the index from the aspect of psychometrics [16]; however, previous intervention studies that investigated the effect of phytoestrogens on menopausal symptoms have used it in recent years [17, 18], so we used the Kupperman index in the present study. The eleven groups of menopausal symptoms in the Kupperman index include vasomotor function, paresthesia, insomnia, nervousness, melancholy, vertigo, weakness, arthralgia and myalgia, headache, palpitation, and formication. The subject reported on the seriousness of the symptom from 0 (none), to 1, 2, or 3 (most serious). Kupperman index totals were the sum of the product of the factors and their seriousness in each group of subjects with menopausal symptoms.

Statistics

Data are presented as means ± standard errors. All data were assessed by Shapiro–Wilk test to check the normality. Differences between pre- and post-menopausal groups in measurement data (the score of hie-sho interview; height, body weight; fat percentage; intake of cholesterol, triglyceride, saturated fatty acid, monounsaturated fatty acid, arachidonic acid, and docosapentaenoic acid; plasma progesterone, triglyceride, HDL- and LDL-cholesterol levels; Kupperman index totals) observed as normality were assessed by Student's *t*-test. Differences between the pre- and post-menopausal groups in measurement data (age; BMI; intake of polyunsaturated fatty acid; plasma estradiol level) observed as disnormality were assessed by Mann–Whitney *U* test. The correlation between the total score of hie-sho interview and each datum observed as normality or disnormality as described above was assessed by Pearson's correlation coefficient and Spearman's rank correlation coefficient, respectively. The statistical processing was performed by using SPSS Statistics 21 software (IBM Corp., Armonk, NY, USA). The null hypothesis was rejected at a level of $p < 0.05$. In the results, the exact p values are shown because of the small sample size.

Results

Score of hie-sho interview

Table 1 lists the 10-question hie-sho interview. Figure 1 shows the percentage of subjects answering 'yes' to hie-sho interview from question no. 1 to no. 10 (Fig. 1a) and the total score of hie-sho interview 'yes' replies (Fig. 1b). The percentage of subjects answering 'yes' to hie-sho interview question no. 8 was the highest in the pre- and post-menopausal groups. All subjects in the pre- and post-menopausal groups answered 'no' to the hie-sho interview question no. 4. It was observed that the percentage of subjects answering 'yes' to hie-sho interview question no. 6 in the pre-menopausal group was greater than that in the post-menopausal group. The total score of the hie-sho interview was not significantly different between the pre- and post-menopausal groups (Fig. 1b).

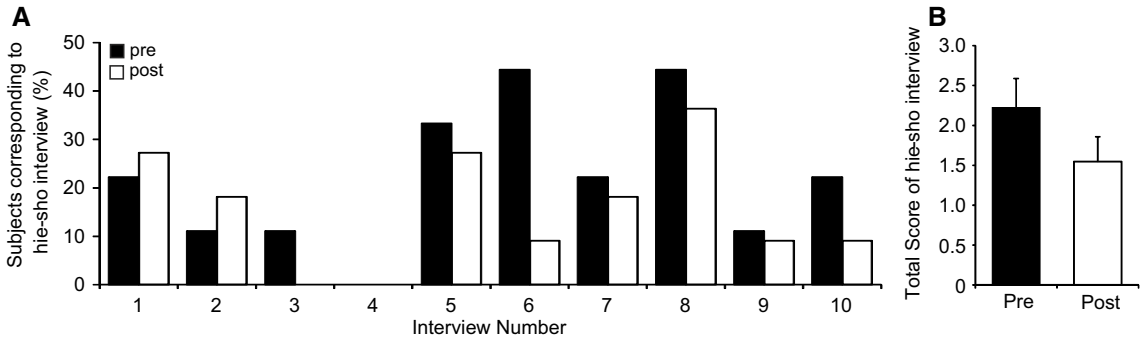

Fig. 1 Subjects answering 'yes' to hie-sho interview questions from item no. 1 to no. 10 (%) (**a**), and the total score of the hie-sho interview (**b**) in the pre- and post-menopausal groups. Values are presented as the mean ± standard error (pre-menopausal group, $n=9$; post-menopausal group, $n=11$)

Table 2 Characteristics of the subjects

	Middle-aged women ($n=20$)	
	Pre ($n=9$)	Post ($n=11$)
Age (years)	47.1 ± 0.9	52.5 ± 0.3*
Height (cm)	156.8 ± 1.4	156.7 ± 1.5
Body weight (kg)	52.9 ± 1.5	53.0 ± 1.1
Percent of fat (%)	27.7 ± 0.6	30.3 ± 0.9*
Body mass index (kg/m²)	21.5 ± 0.5	21.7 ± 0.7

Values are presented as the mean ± standard error (pre-menopausal group, $n=9$; post- menopausal group, $n=11$)

Significant difference between the pre- and post-menopausal groups (*)

Body mass index and body fat percentage

Table 2 shows the characteristics of the subjects. The height, body weight, and BMI were not different between the pre- and post-menopausal women. The percentage of fat in the pre-menopausal group was lower [$t=-2.33$, $df=18$, $p=0.032$] than that in the post-menopausal group. The average age of subjects in the pre-menopausal group was lower [$p=0.000$] than that of the subjects in the post-menopausal group.

Figure 2 illustrates the correlations between the total score of hie-sho interview and the BMI (a) and the percentage of fat (b). Negative correlations were observed between the total score of hie-sho interview and the BMI [$r=-0.722$, $p=0.012$] and percentage of fat [$r=-0.649$, $p=0.031$] in the post-menopausal group.

Plasma estradiol, progesterone, and triglyceride

Figure 3 shows plasma estradiol (A-a), progesterone (A-b), and triglyceride (A-c) concentrations and the correlation between the total score of hie-sho interview and plasma concentrations of estradiol (B-a), progesterone (B-b), and triglyceride (B-c). The plasma HDL-cholesterol and LDL-cholesterol were not different between the pre- and post-menopausal groups (77.0 ± 3.4 and 80.9 ± 5.5 mg/dl; 112.5 ± 9.8 and 124.6 ± 6.4 mg/dl). The plasma estradiol

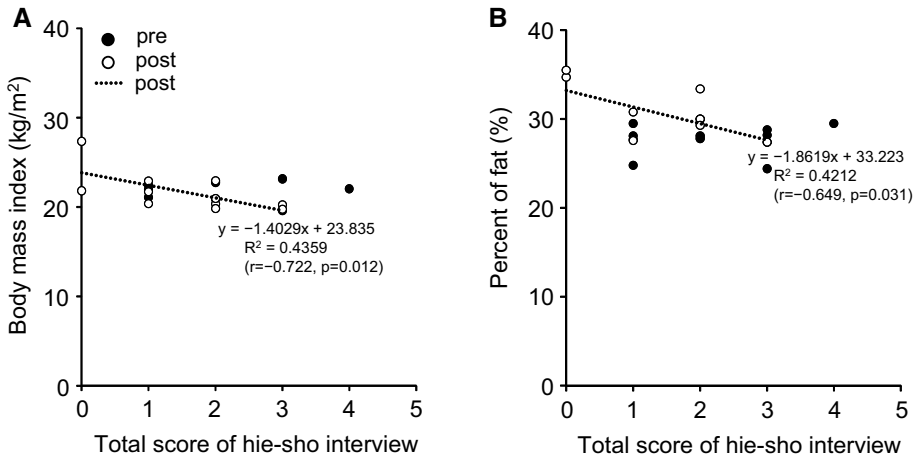

Fig. 2 Relationship between the total score of hie-sho interview and the body mass index (**a**) and the body fat percentage (**b**) in the pre- and post-menopausal groups

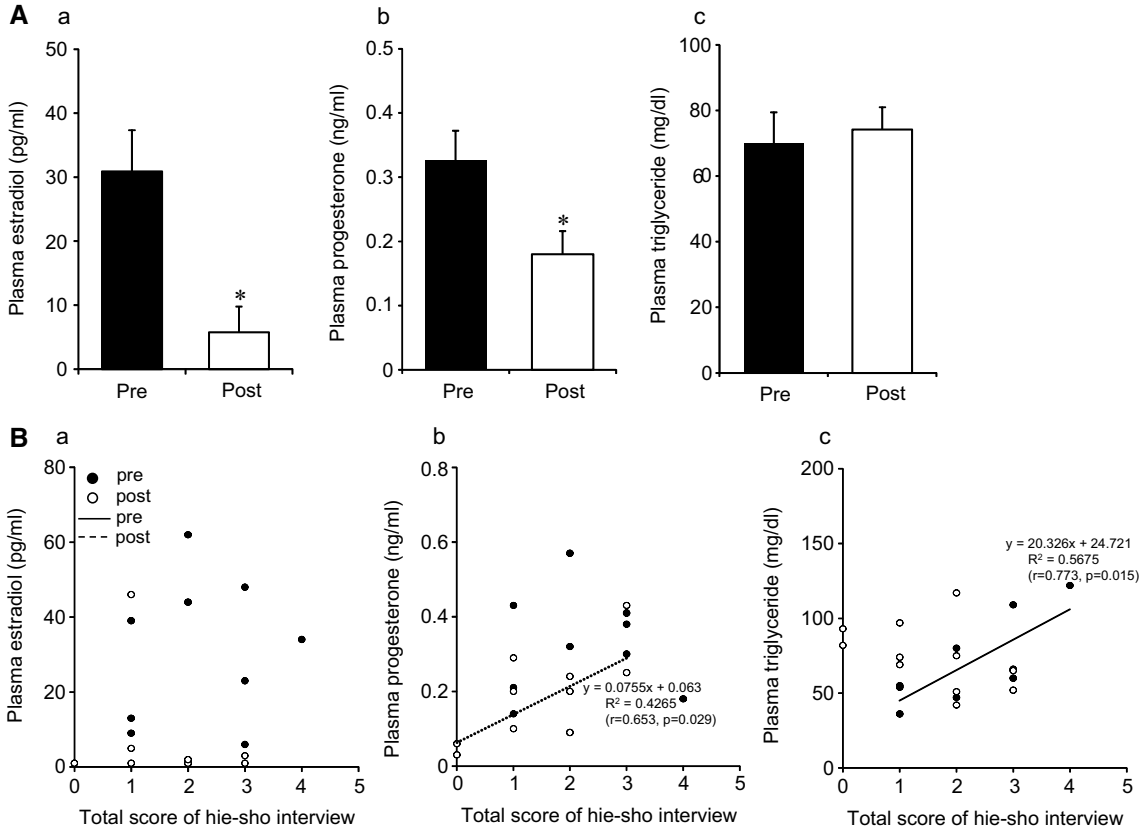

Fig. 3 Plasma estradiol (**A**-**a**), progesterone (**A**-**b**), and triglyceride (**A**-**c**); the relationship between the total score of hie-sho interview and the plasma triglyceride (**B**-**a**), plasma estradiol (**B**-**b**), and plasma progesterone (**B**-**c**) in the pre- and post-menopausal groups. Values are presented as the mean ± standard error (pre-menopausal group, $n = 9$; post-menopausal group, $n = 11$). Significant difference between the pre- and post-menopausal groups (*)

concentration was greater [$p = 0.001$] in the pre-menopausal group than in the post-menopausal group. The plasma progesterone concentration was greater [$t = 2.55$, $df = 18$, $p = 0.020$] in the pre-menopausal group than in the post-menopausal group. No significant difference was observed in the plasma triglyceride concentration between the pre- and post- menopausal groups (Fig. 3A).

A positive correlation was observed between the total score of hie-sho interview and the progesterone concentration [$r = 0.653$, $p = 0.029$] only in the post-menopausal group. A positive correlation was observed between the total score of hie-sho interview and the plasma triglyceride concentration [$r = 0.773$, $p = 0.015$] only in the pre-menopausal group (Fig. 3B).

Intake of fat

Figure 4 shows the intakes of cholesterol (A-a), arachidonic acid (A-b), and docosapentaenoic acid (A-c); the correlation between the total score of hie-sho interview and intakes of cholesterol (B-a), arachidonic acid (B-b), and docosapentaenoic acid (B-c). The intake of triglyceride, saturated fatty acid, monounsaturated fatty acid, and polyunsaturated fatty acid were not significantly different between the pre- and post-menopausal groups (30.2 ± 1.7 and 32.0 ± 1.2 g/1000 kcal; 10.1 ± 1.0 and 10.4 ± 0.6 g/1000 kcal; 12.0 ± 0.7 and 12.7 ± 0.7 g/1000 kcal; 6.6 ± 0.6 and 7.4 ± 0.6 g/1000 kcal). The intakes of cholesterol and arachidonic acid were not different between the pre- and post-menopausal groups. The intake of docosapentaenoic acid in the pre-menopausal group was lower [$t = -2.92$, $df = 13$, $p = 0.012$] than that in the post-menopausal group (Fig. 4A).

A negative correlation was observed between the total score of hie-sho interview and intakes of cholesterol [$r = -0.710$, $p = 0.032$], arachidonic acid [$r = -0.748$, $p = 0.020$], and docosapentaenoic acid [$r = -0.759$, $p = 0.018$] in the pre-menopausal group only (Fig. 4B).

Kupperman index and Kupperman index totals

Figure 5 shows Kupperman index (a), Kupperman index totals (b), and the relationship between the total score of hie-sho interview and Kupperman index totals (c). The Kupperman index for arthralgia and myalgia in the

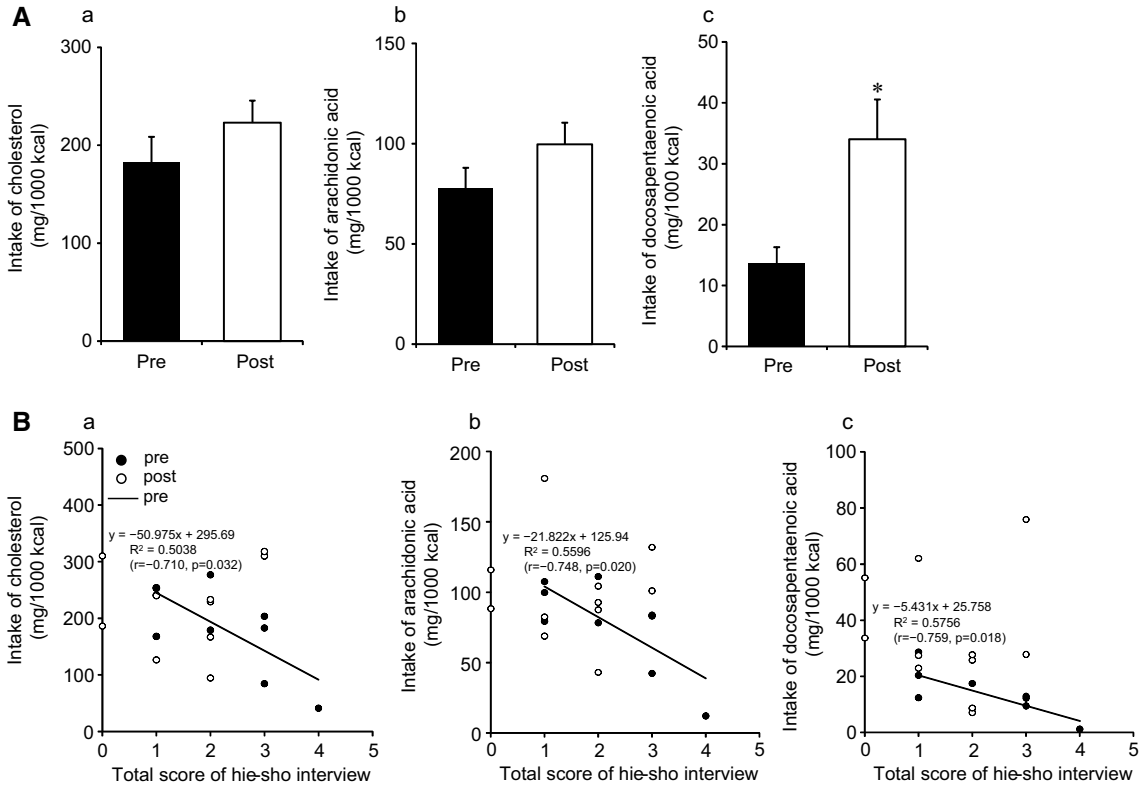

Fig. 4 Intake of cholesterol (**A**-**a**), arachidonic acid (**A**-**b**), and docosapentaenoic acid (**A**-**c**); the relationship between the total score of hie-sho interview and the intake of cholesterol (**B**-**a**), the intake of arachidonic acid (**B**-**b**), and docosapentaenoic acid (**B**-**c**) in the pre- and post-menopausal groups. Values are presented as the mean ± standard error (pre-menopausal group, $n = 9$; post-menopausal group, $n = 11$). Significant difference between the pre- and post-menopausal groups (*)

pre-menopausal group was lower [$p = 0.020$] than that in the post-menopausal group (Fig. 5a). Kupperman index totals were not significantly different between the pre- and post-menopausal groups (Fig. 5b). A positive correlation was observed between the total score of hie-sho interview and Kupperman index totals [$r = 0.819$, $p = 0.007$] only in the pre-menopausal group (Fig. 5c).

Discussion

The present study revealed that in the post-menopausal women, the higher the plasma progesterone concentration was, the higher the hie-sho interview score was. In the pre-menopausal women, the higher the fat intake and the lower the plasma triglyceride concentration was, the lower the hie-sho interview score was. Additionally, the stronger the menopause symptoms assessed by the Kupperman index were, the higher the hie-sho interview score was.

Most of the subjects in the pre- and post-menopausal groups answered 'yes' to the item "need an electric blanket for better sleep in winter?" in the hie-sho interview. Most young women with hie-sho defined by self-reporting (survey respondents $n = 11$, average age 21.7 years) experienced coldness sensation in the toes [19]. Most middle-aged women suffered from a coldness sensation (survey respondents $n = 89$, average age 41 years) every day in the dorsa and soles of their feet [2]. These results indicated that women with hie-sho notably experienced a coldness sensation in their feet. The results of the approximately similar total scores in the hie-sho interview between the pre- and post- menopausal groups revealed that the magnitude of complaints of daily unusual coldness may not have changed between pre- and post-menopausal women.

The post-menopausal group subjects with lower BMI and lower percentage of fat presented with higher hie-sho scores. Several previous studies on young Japanese women with subjective hie-sho have reported that BMI and the percentage of fat in the subjects with hie-sho were lower than in the subjects without hie-sho [5–7, 9]. Similar symptoms to Japanese hie-sho were reported in Switzerland. The BMIs of the subjects with cold extremities (survey respondents $n = 9$, average age 29 years) were lower than the other subjects in the study group (survey respondents $n = 10$, average age 27 years) in Switzerland [20]. A questionnaire for subjects in Basel, Switzerland (survey respondents $n = 2800$,

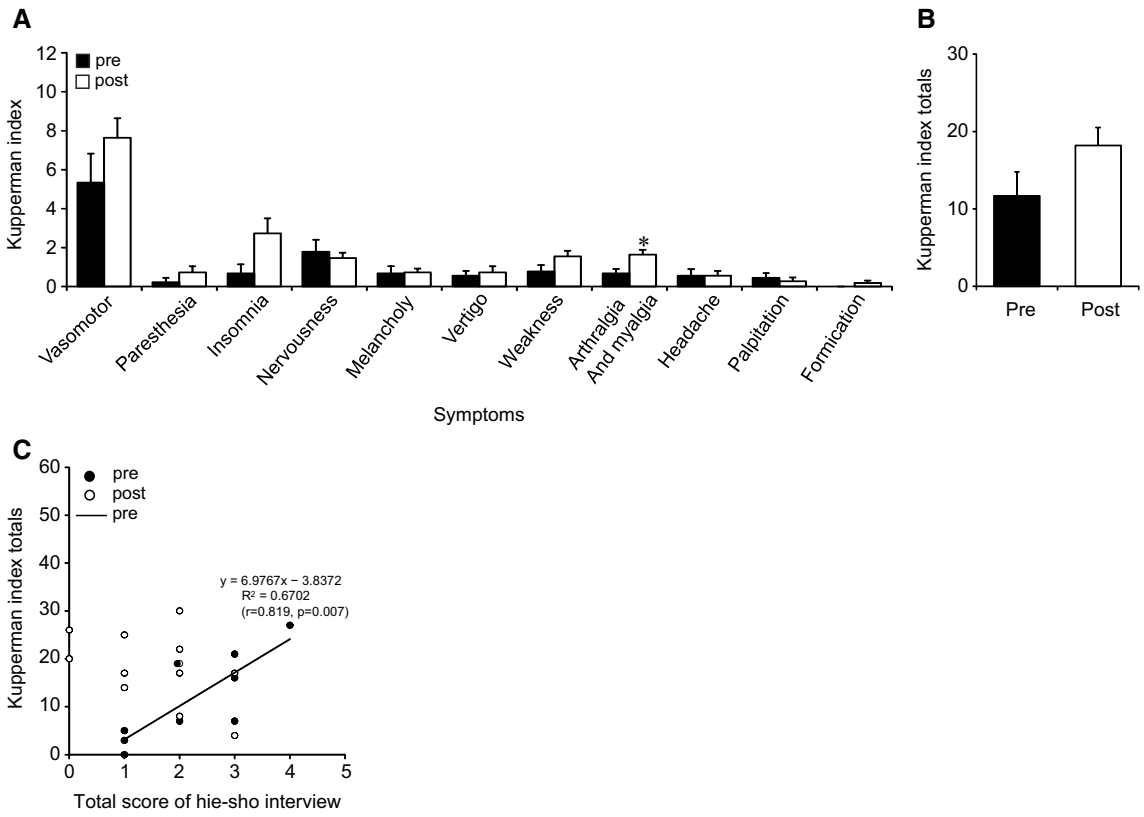

Fig. 5 Kupperman index (**A**), Kupperman index totals (**B**), and the relationship between the total score of hie-sho interview and Kupperman index totals (**C**) in the pre- and post-menopausal groups. Values are presented as the mean ± standard error (pre-menopausal group, $n = 9$; post-menopausal group, $n = 11$). Significant difference between the pre- and post-menopausal groups (*)

age 20–40 years, male = 809, female = 1011) clarified that the subjects who presented with lower BMI experienced cold sensations in their extremities [21]. These results corresponded with our results. The reason that the correlation between BMI, percentage of fat, and hie-sho score was not observed in the pre-menopausal group was unclear; however, the high concentrations of female hormones in the subjects in the pre-menopausal group might cancel the correlation.

Only in the post-menopausal group did subjects with higher plasma progesterone concentration present with a higher hie-sho interview score. Vasoconstriction was enhanced during the luteal phase of the menstrual cycle compared to the early follicular phase, and progesterone enhanced α-adrenergic responsiveness in women [22]. Thus, progesterone might increase adrenergically induced vasoconstriction in the skin, affecting the hie-sho score. The higher the plasma triglyceride was, the higher the hie-sho score was only in the pre-menopausal group. According to the results that E_2 facilitated thermoregulatory behavior in the cold in ovariectomized rats [23], the subjects in the pre-menopausal group that had higher E_2 concentration would be more sensitive to thermal unpleasantness in the cold. In addition, the plasma triglyceride and noradrenaline-induced vasoconstriction of mesenteric arteries in the rats fed a highly palatable diet for 15 weeks was higher than that in rats fed a standard chow [24]. Although the mesenteric arteries and cutaneous vessels are anatomically different, plasma triglyceride is partly related to noradrenaline-induced vasoconstriction, and influenced the hie-sho score in the pre-menopausal group.

In the pre-menopausal group only, the subjects with higher fat intake in the diet had lower hie-sho scores. In a case study of a male subject (age 60 years), administration of the drug named lovastatin for the treatment of hypercholesterolemia, induced a chronic cold sensation; and stopping the drug relieved the cold sensation [25], though the side effect of lovastatin for chronic cold sensation was not reported. These results suggested that the decrease of plasma cholesterol concentration may induce a coldness sensation. The young women with hie-sho (survey respondents $n = 301$) did not like meat, fish, seafood, and egg compared to women without hie-sho (survey respondents $n = 222$), as demonstrated by the questionnaire related to favorite food [10]. These foods contain fats such as cholesterol, arachidonic acid, and docosapentaenoic acid. It can be suggested that fat intake may influence the magnitude of hie-sho. Because

arachidonic acid contributes to the synthesis of PGI2, a vasodilator, in the arachidonate cascade, it may be involved in the correlation of arachidonic acid and the magnitude of complaints of daily unusual coldness. The subjects in the post-menopausal group might be health-conscious because the BMI in the group was within normal limits. If they changed their dietary habits to eat fish, then the intake of docosapentaenoic acid in the post-menopausal group would be higher than that in the pre-menopausal group; however, lower female hormones in the post-group might cancel the effect of docosapentaenoic acid. The abundant plasma female hormones in the pre-menopausal group might have modulated the magnitude of complaints of daily unusual coldness through these fatty acids.

The Kupperman index for arthralgia and myalgia was higher in the post-menopausal group than in the pre-menopausal group. A correlation between the threshold level and tolerance of pain and plasma estradiol concentration in the women with dysmenorrhea (survey respondents $n = 14$) was reported. Thus, estradiol may cause hypoalgesia [26]. The post-menopausal group subjects who presented with low plasma estradiol concentrations might be more sensitive to pain than the subjects in the pre-menopausal group. It was uncertain whether the Kupperman index is different between pre- and post-menopausal women or not, because previous studies have not done that comparison. The climacteric disorders occur at pre- and post-menopause, and continue for between 1 and a few years [27]. Thus, the Kupperman index was not different between pre- and post-groups in the present study. Only in the pre-menopausal group did higher Kupperman index totals, which reflected various menopausal symptoms, correlate with higher hie-sho scores. The results were consistent with the result of the previous survey study; that the physical complaint scores assessed by the Cornell medical index in the women with hie-sho were higher than those in women without hie-sho (survey respondents $n = 318$, average age 26 years) [12]. One possible reason was the lower intake of docosapentaenoic acid in the pre-group. Although the relationship between docosapentaenoic acid and menopausal symptoms was not investigated in the previous studies, the lower docosapentaenoic acid might augment the Kupperman index, and affect the hie-sho score. These results indicate that the effect of menopausal symptoms on the magnitude of complaints of daily unusual coldness was different between the pre- and post-menopausal women.

In the present study, we revealed that the higher the fat intake in the diet and the lower plasma triglyceride was, the lower the hie-sho score was, and the higher the menopausal symptoms were, the higher the hie-sho interview score was in the pre-menopausal women. On the other hand, the higher the plasma progesterone concentration was, the higher the hie-sho score was in the post-menopausal women. The limitations of the present study were a small sample and a cross-sectional design. Because of these limitations, the results cannot be generalized; however, as a pilot study it provides a new aspect in the research of hie-sho.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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