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ORIGINAL ARTICLE

Severity of hot flushes is inversely associated with dietary intake of vitamin B_6 and oily fish

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ABSTRACT

Objectives: This study investigated the links between the severity of vasomotor symptoms (VMS) and the dietary consumption of a variety of nutrients.

Method: A cross-sectional analysis of the first-visit records of 262 women aged 40–65 years was conducted. The severity of their hot flushes (HF) and night sweats (NS) and their dietary consumption of nutrients were evaluated using the Menopausal Health-Related Quality of Life Questionnaire and the brief-type self-administered Diet History Questionnaire, respectively. The relationships between severity of HF/NS and dietary intake were analyzed separately for 43 major nutrients. We then evaluated different food items as sources of the nutrients.

Results: After adjustment for age, body mass index, menopausal status, and background factors significantly related to VMS, only vitamin B_6 (VB_6) was significantly related to severity of HF (adjusted odds ratio per 10 μg/MJ in VB_6 intake, 0.92; 95% confidence interval, 0.86–0.97). Moreover, a significant inverse relationship was found between the consumption of oily fish as a source of VB_6 and the severity of HF.

Conclusions: VB_6 and oily fish intake is inversely associated with the severity of HF in middle-aged women. Therefore, increased intake of VB_6 could help attenuate HF.

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Menopausal symptoms; vasomotor symptoms; night sweats; pyridoxal; fish consumption

Introduction

Vasomotor symptoms (VMS) are among the most common symptoms of menopause and are experienced by approximately 60–80% of women during the menopausal transition[1–3]. VMS are categorized into hot flushes (HF) and night sweats (NS), the latter of which describes perspiration during sleep. Moreover, these symptoms exhibit different prevalence and occurrence patterns[4]. VMS are intolerably severe in 26% of naturally menopausal women; this proportion increases 1.8 times in surgically menopausal women[1]. Additionally, it is well known that the prevalence and duration of VMS differ among racial/ethnic groups[5–7], with Asian women experiencing fewer VMS than Caucasians, African Americans, and Hispanics[2,6]. For example, the prevalence of HF/NS is lower in Japanese (63.1%/46.7%) than in Caucasian (84.0%/76.3%) women[8]. VMS can be accompanied by somatic symptoms as well as sleep and mood disturbance[9], leading to a reduction in quality of life[9,10]. Furthermore, several reports have suggested that VMS are linked to the risk of cardiovascular disease (CVD)[5,11].

Pharmaceutical therapies for VMS include hormone therapy, antidepressants, anticonvulsants, and anticholinergics. However, due to growing concern for the side effects of hormone therapy, especially in patients with hormone-sensitive cancer, such as breast and uterus cancer, research has turned to the effects of nutraceutical approaches on VMS. For example, a wide range of studies have been performed on the effects of the intake of phytoestrogens, including soy isoflavone, red clover, and lignan, on the frequency and severity of VMS[12–18]. However, the effects of the dietary intake of nutrients on VMS have not yet been fully elucidated. The aim of this study is therefore to investigate the relationships between the severity of HF and NS and the dietary intake of a variety of nutrients and food items in Japanese middle-aged women.

Methods

Study population

This cross-sectional study was based on the first-visit records of 700 Japanese women enrolled in the Systematic Health and Nutrition Education Program conducted at the menopause clinic of Tokyo Medical and Dental University, Japan, from January 2009 to August 2017. All women enrolled in this program had been referred to our clinic for the treatment of menopausal symptoms. The aim of the Systematic Health and Nutrition Education Program is to improve physical and psychological health based on the assessment of somatic and mental health status and lifestyles using physical examinations and a variety of questionnaires. Of the 700

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participants during the study period, 307 study participants aged 40–65 years completed both the Menopausal Health-Related Quality of Life Questionnaire (MHR-QOL) and the brief-type self-administered Diet History Questionnaire (BDHQ). Forty-five participants who had already been treated with hormone therapy were excluded. For the remaining 262 study participants, we investigated the individual links between their dietary consumption of different nutrients and food items and the severity of HF and NS.

The research protocol was reviewed and approved by the Tokyo Medical and Dental University Review Board, and written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki.

Measurements

Menopausal status

Participants were classified as: premenopausal if they had regular menstrual cycles; perimenopausal if they had a menstrual period within the past 12 months but had missed periods or had an irregular cycle in the past 3 months; and postmenopausal if they had no menstruation in the past 12 months. Postmenopausal women were also questioned about natural or surgically induced menopause by hysterectomy and/or oophorectomy.

Physical assessments

Participants' body composition, including height, weight, body mass index (BMI), body fat mass, lean body mass, muscle mass, water mass, and basal metabolism, were measured using a body composition analyzer (MC190-EM; Tanita, Tokyo, Japan). Resting energy expenditure was calculated based on respiratory volume using a portable, indirect calorimeter (Metavine-N VMB-005 N; Vine, Tokyo, Japan). Participants' body temperature was also measured with a thermometer and their hand-grip strength was measured with a hand dynamometer (Yagami, Nagoya, Japan). Average hand-grip strength was calculated using the larger value of two measurements for each hand. Additionally, cardiovascular parameters such as systolic and diastolic blood pressure, heart rate, cardio-ankle vascular index, and ankle-brachial pressure index were assessed using a vascular screening system (VS-1000; Fukuda Denshi, Tokyo, Japan).

Lifestyle characteristics

Participants underwent a medical interview for lifestyle factors, which included frequency of alcohol consumption (never, sometimes, daily) and smoking (none, <20, ≥ 20 cigarettes per day), and regular exercise habits (yes, no).

Questionnaire

The MHR-QOL, a modification of the Women's Health Questionnaire[19], was developed and validated in our clinic[20–25]. The MHR-QOL is composed of four categories: physical health, mental health, life satisfaction, and social involvement. HF and NS were rated from 0 (none) to 3 (severe) according to the participant's response to the corresponding items on the MHR-QOL. The severity of the symptoms was rated for their frequency (0 points = 0–1 time per month; 1 point = 1–2 times per week; 2 points = 3–4 times per week; 3 points = almost every day). Furthermore, the individual points of six somatic symptom items and two insomnia symptom items on the MHR-QOL were combined to generate a 'somatic symptom score' and an 'insomnia symptom score', respectively.

The BDHQ, which focuses on the typical Japanese diet, evaluates the intake frequency of 61 food items, including beverages and seasoning, over the previous month. Based on the information provided as responses to the BDHQ, an ad-hoc computer algorithm estimated the daily intake of 96 nutrients after adjustment for total calorie intake. Estimated consumption of food items and nutrients based on the BDHQ has previously been validated by comparison with dietary records using a semi-weighed method[26,27]. In this study, we evaluated 43 major nutrients and 58 food items with high validity (Supplement one).

The Hospital Anxiety and Depression Scale, a reliable screening tool for anxiety and depression, was developed to assess the psychological status of patients with physical symptoms[28]. The Hospital Anxiety and Depression Scale is composed of seven items each for anxiety and depression. Study participants responded to these items using a 4-point Likert scale, and those who received a score of 8–10 points or 11–21 points were considered likely or definitely experiencing anxiety or depression, respectively.

Statistical analysis

Continuous variables are presented as the mean ± standard deviation. The differences between two groups were analyzed using the Mann–Whitney test and the chi-squared test. The Kruskal–Wallis test with the post-hoc Dunn's multiple comparison test were used to evaluate the differences in severity among groups. The stepwise variable selection procedure with a threshold of $p = 0.1$ for variable inclusion and exclusion was performed to assess the nutrients, food items, and background characteristics associated with VMS. Using cut-off points for Pearson or Spearman correlation coefficients $|R|$ of >0.9, the multicollinearity was identified between variables. The relationships between the severity of VMS and the selected nutrients and food items were examined by multivariate logistic regression analysis, after adjustment for the background factors related to VMS. $p < 0.05$ was considered statistically significant. Statistical analysis was performed with GraphPad Prism version 5.02 (GraphPad Software, San Diego, CA, USA) and JMP version 12 (SAS Institute Inc., Cary, NC, USA).

Results

The characteristics of the 262 study participants are shown in Supplement two. Women who had moderate to severe HF and NS accounted for 38.6% and 29.8% of the sample group,

respectively (Table 1). We first investigated the nutrients where intake differed significantly among the four severity groups of HF/NS (Kruskal–Wallis test). Nutrients that showed multicollinearity with others were excluded. Of the remaining nutrients, those that were independently associated with HF/NS were selected using a stepwise variable selection procedure. We found significant relationships between the severity of HF and the intake of vitamin B_5 (pantothenic acid), vitamin B_6 (VB_6), and vitamin D, as well as between NS and phosphorus. Next, we selected the background factors that were significantly related to HF/NS using a stepwise variable selection procedure after excluding multicollinearity. The selected background factors related to HF were systolic blood pressure, heart rate, and the somatic, insomnia, anxiety, and depressive symptom scores, and those related to NS were the somatic and insomnia symptom scores. We performed multivariate logistic regression analysis to determine the independent relationships between the daily intake of the selected nutrients and the severity of HF and NS (Table 2). After adjustment for age, BMI, menopausal status (Model 2), and also selected background characteristics (Model 3), only the intake of VB_6 (10 μg/MJ) exhibited a significant relationship with severity of HF. A higher intake of VB_6 was associated with a lower severity of HF (Model 2, adjusted odds ratio [OR] = 0.94, 95% confidence interval [CI] = 0.90–0.98, $p = 0.002$; Model 3, OR = 0.92, 95% CI = 0.86–0.97, $p = 0.005$). No significant relationship was demonstrated between the daily intake of phosphorus and the severity of NS.

Food items representing the major source for VB_6 were then investigated. We selected five food items (fish with edible bones, oily fish, potatoes, root vegetables, and citrus fruits), for which consumption levels showed significant differences among the four severity groups of HF and which decreased with severity of HF. These five food items contain more than 0.1 mg VB_6 per 100 g of edible portion and exhibited no multicollinearity among them. The relationship between the daily intake of each item and severity of HF was assessed by multivariate logistic regression analysis (Table 3). A significant relationship was observed between the consumption of oily fish (μg/MJ) and the severity of HF after adjustment for age, BMI, menopausal status (Model 2, OR = 0.99, 95% CI = 0.98–1.00, $p = 0.014$), and also selected background factors (Model 3, OR = 0.98, 95% CI = 0.96–0.99, $p = 0.004$).

Table 1. Percentages of women experiencing hot flushes and night sweats.

	Hot flushes		*Night sweats*	
Frequency of VMS	n	%	n	%
0–1 time a month (none)	116	44.3	139	53.1
1–2 times a week (mild)	45	17.2	45	17.2
3–4 times a week (moderate)	28	10.7	27	10.3
Almost every day (severe)	73	27.9	51	19.5

VMS, vasomotor symptoms.

Discussion

In our cross-sectional analysis, the severity of HF was found to be significantly inversely associated with the intake of VB_6 and oily fish in Japanese middle-aged women. VB_6 comprises six chemical compounds: pyridoxine, pyridoxamine, and pyridoxal and their phosphorylated forms pyridoxine 5′-phosphate, pyridoxamine 5′-phosphate, and pyridoxal 5′-phosphate (PLP). PLP is the most active form and plays an enzymatic cofactor role in more than 140 biochemical reactions, such as amino acid and fatty acid metabolism and neurotransmitter biosynthesis[29,30]. VB_6 also plays a key role in the biosynthesis of serotonin, dopamine, and epinephrine. It is therefore expected that VB_6 supplementation would alleviate many neurological disorders, such as schizophrenia and Parkinson's disease[30]. Moreover, VB_6 is an essential coenzyme in the methionine cycle, and its deficiency causes hyperhomocysteinemia, a known CVD risk[30]. The main dietary sources of VB_6 are red pepper, rice grain, garlic, nuts, fish, and meats, according to the Food Composition Database published by the Ministry of Education, Culture, Sports, Science and Technology in Japan[31]. The VB_6 content in oily fish, such as tuna, mackerel, sardine, and mackerel pike (mg/100 g), is approximately 0.6–1.0 mg. The consumption of fish and shellfish in Japan is more than 2.5 times larger than the global average and ranked in the top 10 of countries with a population greater than 1 million, according to the Ministry

Table 3. Relationship between food items and hot flush severity.

		Hot flushes		
Model	*Food item (μg/MJ)*	*OR*	*95% CI*	p-*Value*
Model 1	Fish with edible bones	0.99	0.93–1.00	0.054
	Oily fish	0.99	0.98–1.00	0.015
	Potatoes	1.00	0.99–1.00	0.218
	Root vegetables	1.00	1.00–1.00	0.588
	Citrus fruits	1.00	0.99–1.00	0.065
Model 2	Oily fish	0.99	0.98–1.00	0.014
Model 3	Oily fish	0.98	0.96–0.99	0.004

OR, odds ratio; CI, confidence interval.
Model 1: unadjusted model. Model 2: multivariate logistic regression model, adjusted for age, body mass index, and menopausal status. Model 3: multivariate logistic regression model, adjusted for age, body mass index, menopausal status, and selected background factors.

Table 2. Relationship between daily intake of selected nutrients and severity of vasomotor symptoms.

		Hot flushes				*Night sweats*		
Model	*Nutrient*	*OR*	*95% CI*	p-*Value*		*OR*	*95% CI*	p-*Value*
Model 1	Vitamin B_5 (μg/MJ)	1.11	0.98–1.26	0.100	Phosphorus (mg/MJ)	0.59	0.34–0.99	0.051
	Vitamin B_6 (10 μg/MJ)	0.92	0.87–0.97	0.004				
	Vitamin D (ng/MJ)	0.98	0.97–1.00	0.054				
Model 2	Vitamin B_6	0.94	0.90–0.98	0.002				
Model 3	Vitamin B_6	0.92	0.86–0.97	0.005				

OR, odds ratio; CI, confidence interval.
Model 1: unadjusted model. Model 2: multivariate logistic regression model, adjusted for age, body mass index, and menopausal status. Model 3: multivariate logistic regression model, adjusted for age, body mass index, menopausal status, and selected background factors.

of Agriculture, Forestry and Fisheries[32]. In addition, Japanese people consume a large amount of tuna and mackerel pike in the category of fish and shellfish[32], and oily fish may be one of the major sources of VB_6 in Japanese cuisine. In America and European countries, cod, Alaskan pollock, and salmon, which are low in fat, are often eaten[33,34]. A lot of canned tuna is also consumed[34]; however, this contains only one-fifth of the VB_6 of raw tuna[31]. High consumption of oily fish could therefore contribute to the lower prevalence of VMS in Japanese women than in North American and European women. The recommended dietary allowance and tolerable upper intake level of VB_6 in adult women are 1.2 mg/day and 40–45 mg/day, respectively, according to the dietary reference intakes defined by the Ministry of Health, Labor and Welfare in Japan[35]. In our study participants, the estimated daily intake of VB_6 in the asymptomatic and the most severe groups was calculated as 1.4 ± 0.6 mg/day and 1.1 ± 0.4 mg/day, respectively.

Discussion of the mechanism underlying the pathology of VMS has mainly been focused on the dysfunction of thermoregulatory response; that is, the upper and lower thresholds of the thermoregulatory zone shift, leading to perspiration and shivering[9,36]. Recently, several reports have demonstrated the central pathogenic mechanism of VMS and a novel treatment strategy. KNDy neurons in the arcuate nucleus of the hypothalamus colocalize kisspeptin, neurokinin B, and dynorphin receptors, and have been shown to play a key role in neuroendocrine regulation for the reproductive axis[37,38]. During the menopausal transition, the absence of estrogen negative feedback due to decreased levels of estrogen, which negatively regulates KNDy neurons[39], has been thought to be linked with hypertrophy of KNDy neurons and increased NK3 receptors (NK3Rs) and their activity[39,40]. Hyperactivity of KNDy neurons and the activation of heat dissipation pathways through neurokinin B/NK3R signaling are believed to trigger VMS[41,42]. Several reports have shown that NK3R antagonists attenuate the severity and frequency of VMS and could be safe and effective for symptom relief[43,44]. Gottsch *et al.*[45] demonstrated that γ-aminobutyric acid, which is synthesized by the PLP-dependent enzyme glutamic acid decarboxylase, strongly inhibits KNDy neurons[45–47]. Therefore, increased intake of VB_6 (PLP) could raise γ-aminobutyric acid and lower the activity of KNDy neurons, leading to the attenuation of VMS.

This study has several limitations. First, the study population was relatively small and consisted only of Japanese women. It is not clear that our findings apply to other race/ethnic groups. Additionally, the causal relationship between the severity of HF and the dietary intake of VB_6 remains unknown due to the cross-sectional nature of our study. The severity of VMS was categorized only according to the subjective frequency, and the intensity and duration were not investigated. Finally, although we assessed the daily estimated consumption of nutrients and food items with the BDHQ, we did not evaluate the serum concentration of VB_6.

Despite these limitations, this study has several strengths and novel features. We simultaneously analyzed the consumption of as many as 43 nutrients and 58 food items using the BDHQ. Furthermore, background factors associated with VMS were investigated according to a variety of background characteristics, including body composition, CVD parameters, and body temperature. To the best of our knowledge, this is the first report on the relationship between intake of VB_6 and severity of HF.

In conclusion, the consumption of VB_6 and oily fish was shown to be inversely related to the severity of HF. Therefore, increased intake of VB_6 and its sources (i.e. oily fish) may represent a simple new nutritional approach to relieving HF in middle-aged women.

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