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Dietary vitamin D intake, 25-hydroxyvitamin D_3 levels and premenstrual syndrome in a college-aged population☆

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ABSTRACT

High dietary intake of vitamin D may reduce the risk of premenstrual syndrome (PMS), perhaps by affecting calcium levels, cyclic sex steroid hormone fluctuations, and/or neurotransmitter function. Only a small number of previous studies have evaluated this relationship and none have focused on young women. We assessed this relationship in a cross-sectional analysis within the UMass Vitamin D Status Study. Between 2006 and 2008, 186 women aged 18–30 (mean age = 21.6 years) completed a validated food frequency questionnaire, additional questionnaires to assess menstrual symptoms and other health and lifestyle factors, and provided a fasting blood sample collected during the late luteal phase of their menstrual cycle. Among all study participants, results suggested the possibility of an inverse association between intake of vitamin D from food sources and overall menstrual symptom severity, though were not statistically significant; mean intakes in women reporting menstrual symptom severity of none/minimal, mild, and moderate/severe were 253, 214, and 194 IU/day, respectively ($P = 0.18$). From among all study participants, 44 women meeting standard criteria for PMS and 46 women meeting control criteria were included in additional case–control analyses. In these women, after adjustment for age, body mass index, smoking status and total calcium intake, higher intake of vitamin D from foods was associated with a significant lower prevalence of PMS. Women reporting vitamin D intake from food sources of ≥100 IU/day had a prevalence odds ratio of 0.31 compared to those reporting <100 IU/day (95% confidence interval = 0.10–0.98). Late luteal phase 25-hydroxyvitamin D_3 levels were not associated with prevalent PMS. Results from this pilot study suggest that a relationship between vitamin D and PMS is possible, though larger studies are needed to further evaluate this relationship and to investigate whether 25-hydroxyvitamin D_3 levels in the follicular or early luteal phases of the menstrual cycle may be related to PMS risk.

1. Introduction

Moderate-to-severe premenstrual syndrome (PMS) affects up to 20% of reproductive age women and is associated with substantial levels of impairment [1]. The most common symptoms of PMS include irritability, mood swings, anxiety, depression, breast tenderness, bloating, and headaches. While many pharmaceutical treatments for PMS have been evaluated, all have significant limitations and none has a reported efficacy greater than 60–70%. Because of the substantial limitations of available treatments, it is important to identify ways to prevent the initial development of this disorder.

While the etiology of PMS remains largely unclear, evidence from multiple sources suggests that vitamin D may play a role in its development and/or the experience of symptoms. Both diet and sunlight contribute to circulating levels of plasma vitamin D metabolites. Dietary intake of fortified dairy foods and cereals, some types of fish, multivitamins and calcium/vitamin D supplements contribute importantly to vitamin D in elderly populations and those with low ambient sunlight exposure [2]. In populations with ample sun exposure, cutaneous conversion of 7-dehydrocholesterol to previtamin D after exposure to solar UV radiation provides the greater source. Previtamin D from both diet and cutaneous production is hydroxylated in the liver into 25-hydroxyvitamin D_3 (25(OH)D_3), the metabolite circulating in the greatest concentration. 25(OH)D_3 is then further hydroxy-

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Table 1
Association of vitamin D intake and serum 25OHD$_3$ levels with overall menstrual symptom severity and prevalence of premenstrual syndrome (PMS) in the pilot UMass Vitamin D Status Study (2006–2008).

Vitamin D measurement	Overall menstrual symptom severity			*P*-Value
	None/minimal (n = 48) Mean (SE)	Mild (n = 107) Mean (SE)	Moderate/severe (n = 31) Mean (SE)	
Total vitamin D intake (IU/day)				
Model 1[a]	416 (39.0)	360 (26.1)	365 (48.4)	0.48
Model 2[b]	364 (36.8)	378 (23.8)	384 (44.4)	0.93
Vitamin D from foods (IU/day)				
Model 1[a]	281 (22.5)	205 (15.1)	179 (28.0)	0.006
Model 2[b]	253 (21.3)	214 (13.6)	194 (25.3)	0.18
25OHD (nmol/L)				
Model 1[c]	75.2 (3.8)	80.2 (3.1)	82.9 (7.4)	0.49
Model 2[d]	75.5 (3.9)	80.1 (3.1)	82.5 (6.9)	0.57

Vitamin D measurement	PMS			
	Cases	Controls	RR (95% CI) Model 1	RR (95% CI) Model 2
Total vitamin D intake (IU/day)				
<100	11	5	1.0	1.0
≥100	33	41	0.38 (0.11–1.15)[a]	0.34 (0.09–1.28)[b]
Vitamin D from food sources only (IU/day)				
<100	16	8	1.0	1.0
≥100	28	38	0.34 (0.12–0.95)[a]	0.31 (0.10–0.98)[b]
25OHD (nmol/L)				
<60	11	13	1.0	1.0
≥60	33	33	1.18 (0.46–3.02)[c]	1.29 (0.45–3.74)[d]

[a] Adjusted for total calorie intake only.
[b] Adjusted for total calorie intake, age, body mass index, smoking history, total calcium intake, and physical activity.
[c] Unadjusted; for mean 25(OH)D levels, standard deviation is presented instead of standard error.
[d] Adjusted for age, season, body mass index, smoking history, total calcium, and physical activity.

lated to 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), in the kidney and in target tissues including the brain, breast and endometrium. $1,25(OH)_2D_3$ is the biologically active metabolite that binds to nuclear vitamin D receptors in target tissues.

It has been suggested that women with luteal phase symptoms consistent with PMS may be experiencing vitamin D deficiency, or related conditions of calcium dysregulation and hyperparathyroidism [3] but few studies have addressed this. In a sub-study within the prospective Nurses' Health Study II (NHSII), high total vitamin D intake was associated with a significant 41% lower risk of PMS, while high vitamin D from food sources only was associated with a significant 31% lower risk [4]. Results from this study are provocative and raise several questions. For example, it is unknown whether vitamin D may be associated with overall severity of menstrual symptoms in a general population, and whether serum $25(OH)D_3$ levels, which better reflect vitamin D status than dietary intake alone, are associated with PMS. Therefore, we have evaluated these relationships in a pilot study of college-aged women in Massachusetts, USA.

2. Materials and methods

2.1. Study population

We conducted a cross-sectional analysis among members of the University of Massachusetts Vitamin D Status Study. Participants were 186 healthy, premenopausal women aged 18–30 living in the Amherst, MA, USA area (latitude = 42.380N), and were enrolled in the study between March 2006 and June 2008. Women were ineligible if they: (1) were pregnant or not currently menstruating; (2) were experiencing untreated depression; (3) reported a history of high blood pressure or elevated cholesterol, kidney or liver disease, bone disease such as osteomalacia, digestive disorders, rheumatologic disease, multiple sclerosis, thyroid disease, hyperparathyroidism, cancer, type 1 or type 2 diabetes, or polycystic ovaries; or (4) were taking corticosteroids, anabolic steroids, anticonvulsants, cimetidine, or propranolol.

2.2. Assessment of dietary vitamin D intake and plasma 25(OH)D_3 levels

All study measurements were completed in a single clinic visit scheduled for the late luteal phase of each participant's menstrual cycle. We assessed each participant's frequency of intake of 131 food items and supplements in the previous 2 months using a modified version of the Harvard Food Frequency Questionnaire (FFQ), which has been extensively validated for use in US women [5]. Vitamin D-rich foods items included on the questionnaire included fortified dairy foods, orange juice and breakfast cereals, dark meat fish, multivitamins, and other supplements containing vitamin D. FFQs were analyzed at Harvard University, and vitamin D intake was calculated by multiplying the frequency of intake of a specified portion size of each food queried by its vitamin D content and then summing across all food items.

Each participant also provided a fasting blood sample at their clinic visit. Blood samples were processed and stored at −80 °C immediately, usually within 2 h of draw. Serum $25(OH)D_3$ concentrations were determined using a commercially available radioimmunoassay kit from DiaSorin (MN, USA), which has been previously validated [6]. Gamma irradiation of I^{125} (in counts per minute; CPM) was quantified using a Beckman Gamma 4000 counter (Beckman Coulter, California, USA), and CPM were converted into concentration units using GraphPad Prism version 4.00 for Windows (GraphPad Software, San Diego, CA).

2.3. Assessment of menstrual symptoms and premenstrual syndrome

We collected information on current menstrual symptom experience by questionnaire based on the Calendar of Premenstrual Experiences questionnaire designed by Mortola et al. [7] and similar to that used in the NHSII [4,8]. Participants were given a list of 26 menstrual symptoms and asked to indicate which they had experienced "most months of the year for at least several days before [their] menstrual period begins" and to indicate the severity of the each symptom. Additional questions asked about the timing of symptom occurrence during the menstrual cycle. We further asked women to classify their overall symptom severity as: "minimal (no effect on normal activities)"; "mild (noticeable, but not troublesome)"; "moderate (interferes with normal activities)"; or "severe (intolerable, prevents normal activities)". To evaluate the effect of menstrual symptoms on interpersonal relationships and life activities, we asked participants to indicate whether or not they experienced relationship discord with a spouse or partner, difficulties in parenting, poor work performance/attendance, and/or social isolation as a result of their symptoms, and if so, to classify the severity of the problem as mild, moderate or severe. We then asked if a clinical diagnosis of PMS had ever been made.

We used questionnaire responses to identify women meeting criteria for PMS, similar to those used by Mortola et al. [7]. A women was considered as experiencing PMS if she reported: (1) at least one physical and one affective menstrual symptom; (2) overall symptom severity of "moderate" or "severe", impact of symptoms on life activities and relationships of "moderate" or "severe", or one or more individual symptoms rated as "severe"; (3) symptoms being within 14 days of the start of menses; (4) symptoms end within 4 days of the start of menses; (5) symptoms are absent in the week after menses. Overall 44 women (24%) met these criteria. We also identified women to serve as controls. Controls were women who reported: (1) overall symptom severity of "none" or "mild" for all individual symptoms; (2) overall symptom severity of "none", "minimal" or "mild"; (3) impact of symptoms on life activities and relationships of "not a problem" or "mild" for all items; and (4) confirmed no previous clinical diagnosis of PMS. Overall, 46 women met these criteria.

2.4. Assessment of covariates

We collected information on lifestyle and demographic factors by self-reported questionnaire, including smoking status and use of oral contraceptives and selective serotonin reuptake inhibitors (SSRIs). Weight and height were directly measured and used to calculated body mass index (BMI; weight (kg)/height $(m)^2$). To measure physical activity, we asked participants to report the time they spent each week engaged in specific activities including walking, jogging, running, bicycling, aerobics/dancing, tennis/racket sports, swimming, yoga/Pilates, and weight training. These questions were based on those used in the NHSII and have been previously validated in that population [9]. We then calculated total MET-hours per week of activity [10]. Total calorie intake and dietary intake of calcium and other nutrients was assessed with the study FFQ. To measure sun exposure, we asked about time spent outdoors wearing minimal clothing, use of sunscreen, recent travel to sunny locations and use of tanning beds.

2.5. Statistical analysis

All analyses were completed using SAS (version 9.0). We compared demographic and lifestyle characteristics of PMS cases and controls using *t*-tests and chi-squared tests. We first assessed the relationship between 3 categories of overall menstrual symptom severity (none/minimal vs. mild vs. moderate/severe) and vitamin D in all 186 study members using generalized linear models adjusted for potential confounders. Both vitamin D from foods and supplements combined and from food sources only were evaluated, and all analyses were adjusted for total calorie intake. In sub-analyses limited to the 44 women meeting criteria for PMS and 45 controls, we calculated multivariable odds ratios for prevalent PMS and 95% confidence intervals using logistic regression. Multivariable analyses were then repeated to assess the association of $25(OH)D_3$ levels with menstrual symptoms and PMS prevalence.

3. Results

The mean age of our study population was 21.6 (SD = 3.2) years. Mean BMI was 22.8 (2.9) kg/m^2 and women averaged 56.8 (49.2) MET-hours per week of physical activity. PMS cases were significantly more likely to have ever smoked cigarettes compared to controls (14.4% vs. 2.2%; $P = 0.002$). PMS cases and controls did not differ significantly by total calorie intake, total calcium intake, BMI, oral contraceptive use, SSRI use, MET-hours per week of activity or aspects of sun exposure.

Among all study participants, we observed the suggestion of an inverse relationship between intake of vitamin D from food sources and menstrual symptom severity, though results in multivariable analysis did not reach statistical significance (Table 1). After adjustment for total calories, age, BMI, smoking history and calcium intake, mean intake of vitamin D from foods in women reporting none/minimal, mild and moderate-to-severe menstrual symptoms were 253, 214 and 194 IU/day, respectively ($P = 0.18$). We did not find total vitamin D intake to vary significantly by menstrual symptom severity. After adjustment for age, BMI, smoking history, calcium intake, physical activity and season, $25(OH)D_3$ levels in women reporting none/minimal, mild and moderate/severe menstrual symptoms were 75.5, 80.1 and 82.5 nmol/L, respectively ($P = 0.57$).

In analyses limited to women meeting PMS case or control criteria, vitamin D intake from foods was significantly associated with prevalent PMS. In multivariable analyses, women reporting $\geq$100 IU/day of vitamin D from food sources only had an OR of 0.31 (95% CI = 0.10–0.98) compared to those reporting <100 IU/day. Results for total vitamin D intake were similar in magnitude but were not statistically significant. We did not find these relationships to be significantly modified by dietary calcium intake, though results were somewhat stronger in women reporting low calcium intake (results not shown).

Finally, we did not find $25(OH)D_3$ levels to be associated with risk of prevalent PMS. Compared to women with $25(OH)D_3$ levels <60 nmol/L, those with $\geq$60 nmol/L had an OR of 1.29 (95% CI = 0.45–3.74).

4. Discussion

In our pilot study in young women, we observed evidence that vitamin D intake may be inversely associated with prevalent PMS, and perhaps with menstrual symptom severity in general. In contrast, late luteal phase serum $25(OH)D_3$ levels were not associated with either outcome.

High dietary intake of vitamin D may reduce the risk of PMS perhaps by affecting calcium levels [2], cyclic sex steroid hormone fluctuations [3], and/or neurotransmitter function [11]. Vitamin D has been observed to fluctuate across the menstrual cycle along with changes in estradiol at ovulation and during the luteal phase in several but not all studies [3]. Thys-Jacobs and Alvir found serum 25(OH)D levels to be significantly lower in cases across 3 phases of the menstrual cycle [12], while $1,25(OH)_2D$ levels were

non-significantly higher in cases at all phases. In a recent larger study, 25(OH)D levels were non-significantly lower in women with premenstrual dysphoric disorder compared to controls across 5 menstrual cycle phases [13]. In contrast, 1,25$(OH)_2$D levels increased significant across the menstrual cycle in controls but declined at ovulation in cases to levels significantly lower than controls. It has been suggested that women with PMS may have increased 1alpha-hydroxyase activity and increased metabolism of 25(OH)D to 1,25$(OH)_2$D in the luteal phase [12], but this has not been well evaluated in human studies.

There are several possible explanations for the difference in our results for vitamin D intake vs. 25$(OH)D_3$ levels. First, as ours was a relatively small study, this finding may be due to chance. Alternatively, in our population the correlation between 25$(OH)D_3$ levels and total vitamin D intake was relatively weak ($r = 0.18$; $P = 0.01$). It is possible that a protective effect of high dietary vitamin D intake may reflect residual confounding by other factors associated with PMS risk. However, with the exception of smoking, cases and controls did not differ in terms of most characteristics previously associated with PMS including BMI, calcium intake, and oral contraceptive use [4,14], and we adjusted for these factors in our analysis. Alternatively, laboratory error in 25$(OH)D_3$ measurements may have attenuated results. However, serum 25$(OH)D_3$ levels were positively correlated with physical activity ($r = 0.16$; $P = 0.04$) and inversely correlated with BMI ($r = -0.10$; $P = 0.18$) in our population, supporting the overall validity of our assay.

Strengths of our study include a comprehensive assessment of dietary vitamin D intake using a validated questionnaire, and measurement of numerous lifestyle and demographic factors. In addition, our method for assessing PMS in population-based studies has been validated previously and found to well differentiate women with moderate-to-severe menstrual symptoms consistent with PMS from women with few symptoms [8].

Results from this pilot study suggest that a relationship between vitamin D and PMS is possible. Larger studies are needed to further evaluate this relationship and to investigate whether 25$(OH)D_3$ levels at different phases of the menstrual cycle are related to PMS risk in young women.

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References

[1] U. Halbreich, The etiology, biology and evolving pathology of premenstrual syndromes, Psychoneuroendocrinology 28 (Suppl. 3) (2003) 55–99.
[2] M.F Holick, Vitamin D: a D-Lightful health perspective, Nutr. Rev. 66 (10 Suppl. 2) (2008) S182–S194.
[3] S. Thys-Jacobs, Micronutrients and the premenstrual syndrome: the case for calcium, J. Am. Coll. Nutr. 19 (2) (2000) 220–227.
[4] E.R. Bertone-Johnson, S.E. Hankinson, A. Bendich, S.R. Johnson, W.C. Willett, J.E. Manson, Calcium and vitamin D intake and risk of incident premenstrual syndrome, Arch. Intern. Med. 165 (11) (2005) 1246–1252.
[5] W.C. Willett, L. Sampson, M.J. Stampfer, et al., Reproducibility and validity of a semiquantitative food frequency questionnaire, Am. J. Epidemiol. 122 (1) (1985) 51–65.
[6] B. Hollis, Comparison of commercially available (125)I-based RIA methods for the determination of circulating 25-hydroxyvitamin D, Clin. Chem. 46 (10) (2000) 1657–1661.
[7] J.F. Mortola, L. Girton, L. Beck, S.S.C. Yen, Diagnosis of premenstrual syndrome by a simple, prospective, and reliable instrument: the calendar of premenstrual experiences, Obstet. Gynecol. 76 (2) (1990) 302–307.
[8] E.R. Bertone-Johnson, S.E. Hankinson, S.R. Johnson, J.E. Manson, A simple method for assessing premenstrual syndrome in large prospective studies, J. Reprod. Med. 52 (9) (2007) 779–786.
[9] A.M. Wolf, D.J. Hunter, G.A. Colditz, et al., Reproducibility and validity of a self-administered physical activity questionnaire, Int. J. Epidemiol. 23 (5) (1994) 991–999.
[10] B.E. Ainsworth, W.L. Haskell, A.S. Leon, et al., Compendium of physical activities: classification of energy costs of human physical activities, Med. Sci. Sports Exerc. 25 (1) (1993) 71–80.
[11] E.R. Bertone-Johnson, Vitamin D and the occurrence of depression: causal association or circumstantial evidence? Nutr. Rev. 67 (8) (2009) 481–492.
[12] S. Thys-Jacobs, M.J. Alvir, Calcium-regulating hormones across the menstrual cycle: evidence of a secondary hyperparathyroidism in women with PMS, J. Clin. Endocrinol. Metab. 80 (7) (1995) 2227–2232.
[13] S. Thys-Jacobs, D. McMahon, J.P. Bilezikian, Cyclic changes in calcium metabolism across the menstrual cycle in women with premenstrual dysphoric disorder, J. Clin. Endocrinol. Metab. 92 (8) (2007) 2952–2959.
[14] E.R. Bertone-Johnson, S.E. Hankinson, S.R. Johnson, J.E. Manson, Cigarette smoking and the development of premenstrual syndrome, Am. J. Epidemiol. 168 (8) (2008) 938–945.