Vitamin D Extended Abstract

Primary Literature: Article #1

Bertone-Johnson ER, Chocano-Bedoya PO, Zagarins SE, Micka AE, Ronnenberg AG. Dietary vitamin D intake, 25-hydroxyvitamin D_3 levels and premenstrual syndrome in a college-aged population. Journal of Steroid Biochemistry & Molecular Biology. 2010; 121:434–437

Study Objectives

To determine whether Vitamin D is associated with the severity of menstrual symptoms and if 25(OH) D_3 levels, which reflects vitamin D status, are associated with PMS.

Methods

- **Design:** Cross-sectional analyses within the University of Massachusetts Vitamin D Status Study
- **Allocation:** N/A
- **Blinding:** N/A
- **Follow-up Period:** N/A
- **Setting:** The measurements that were used in this study were completed in a single clinic visit scheduled for the late luteal phase of each participant's menstrual cycle.
- **Participants:** 186 premenopausal women aged 18–30

  Exclusion criteria: (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.
- **Intervention:**

- Food was assessed using a modified version of the Harvard Food Frequency Questionnaire (FFQ).
- Participants gave a fasting blood sample at the same clinic visit
- Serum 25 (OH) D_3 levels were processed within 2 hours using a radioimmunoassay kit.
- Menstrual symptoms were assessed via a questionnaire based on the Calendar of Premenstrual Experiences Questionnaire
- 44 of the 186 participants were considered to have PMS (24%) and 46 of the 186 (25%) participants were considered control subjects.

- **Outcomes:** N/A
- **Patient follow-up:** N/A

Main Results

- In analyses of the entire study population:
  - Dietary vitamin D intake in women reporting menstrual symptom severity of none/minimal, mild, and moderate/severe were 253, 214, and 194 IU/day, respectively ($P = 0.18$)
  - 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 participants meeting PMS criteria and control criteria:
  - Dietary Women reporting vitamin D intake from food sources of ≥100 IU/day had a prevalence odds ratio of 0.31 vs. those reporting <100 IU/day (95% CI= 0.10–0.98)
  - Results for total vitamin D intake was not statistically significant
  - 25(OH)D_3 levels were not associated with the risk of PMS

Conclusion

Based on the results of the study, the amount of dietary vitamin D may be associated with the severity of PMS. Women having more than 100 IU/day of vitamin D have a prevalence odds ratio of 0.31 compared to those women who do not consume more than

100 IU/day of vitamin D from food. The same conclusion cannot be drawn for total vitamin D intake from all sources (i.e. food, supplement, sun exposure) and serum 25 $(OH)D_3$ levels as the results were not clinically significant (the confidence interval passed through1).

Critical Appraisal

Overall the study was done relatively well. The method section provided sufficient information and was organized. The criterion for a PMS diagnosis was clearly written as well as the exclusion criteria for the participants. The researchers used a validated food questionnaire and described how the blood samples were processed and analyzed.

The biggest drawback with this study was that it was not randomized or double-blinded. The study was a cross sectional study so the only conclusion that can be made with this study is that dietary vitamin D may be associated with PMS symptoms. In this, readers don't know how useful vitamin D is for PMS, what amount is necessary, or if dietary vs. supplement intake is better. The population size was not big and the researchers didn't describe the demographics of the participants. This makes it difficult to extrapolate the results to other people. The results of the study are also deceiving as not all the results were adjusted for the same variables. For example, vitamin D from food sources was only adjusted for calorie intake. This is interesting because this was the only category that the researchers said had a statistically significant result.

Critical Appraisal Conclusion: After critically appraising the article, the only conclusion that can be made is that dietary vitamin D may be associated with the severity of PMS symptoms. Further research needs to be completed to determine how much vitamin D is needed and if supplemental vitamin D can also be used to reduce the severity of PMS.

Primary Literature: Article # 2

Khajehei M, Abdali K, Parsanezhad ME, Tabatabaee HR. Effect of treatment with dydrogesterone or calcium plus vitamin D on the severity of premenstrual syndrome. International Journal of Gynecology and Obstetrics. 2009; 105: 158–161

Study Objective

To link the consequence of dihydrogesterone and calcium plus vitamin D on women who have premenstrual syndrome.

Methods

- **Design**
  - Randomized, placebo- controlled study
- **Allocation**
  - Women were randomly allocated to 1 of 3 study groups consisting of 60 participants: 1) placebo 2) dydrogesterone 3) calcium+ vitamin D
    - A number was assigned to each blank questionnaire and then 3 numbers were randomly chosen from those assigned numbers to designate the first persons to join each of the 3 groups.
    - The177 remaining participants were divided into 59 groups consisting of 3 persons.
    - Each of these 3 participants was randomly assigned to one of the 3 study groups.
- **Blinding**
  - Double blinded
- **Follow-up period**
    - Follow-up period: 4 months
    - In first 2 months, patients recorded their symptoms on a daily symptom rating (DSR form) (pretreatment period)
    - In the second 2 months, patients were asked to fill out the same DSR form (treatment period)
- **Setting**
  - Shiraz University
- **Participants**
  - 180 female university students
  - Inclusion criteria: 1) having regular menstrual cycles (2) not taking certain medications (i.e. hormonal contraceptives); (3) not having contraindications to taking dydrogesterone or supplements containing calcium or vitamin D; (4) meeting the American College of Obstetrics and Gynecology and American Psychiatric Association diagnostic criteria for PMS

(5) diagnostic criteria confirmed by daily symptom ratings during at least 2 consecutive cycles; (6) symptoms significantly impact work, school activities and relationships; (7) symptoms not an exacerbation of another condition (8) not having a diet rich calcium and/or vitamin D.

- **Interventions**
  - Randomly assigned to 5mg of dydrogesterone, 500mg calcium and 200mg of Vitamin D, or placebo taken twice a day from the 15th- 24 day of their cycle
- **Patient Follow-up**
  - 14 participants dropped out during the pre-treatment phase and 6 participants dropped out of the treatment period. These participants were not included in the analyses.

Results

- In the pre-treatment phase, patient's symptoms were mostly severe in all 3 groups. After treatment, symptoms were mostly moderate in the dydrogesterone group and calcium plus vitamin D but mostly severe in the placebo group.
- Patients had less severe symptoms after the intervention of dydrogesterone and calcium plus vitamin (4.64% and 4.20%, respectfully) compared to placebo (3.42%).
- The main side effects were constipation and nausea and the numbers were similar in the dydrogesterone and calcium plus vitamin D group.

Conclusions

Based on the results, dydrogesterone and calcium plus Vitamin D were more effective than placebo in regards to treating the severity of premenstrual syndrome. Moreover, the 2 treatments were similar in the % by which the average severity of the symptoms was decreased.

Critical Appraisal

The study design was good as it was a randomized, double-blinded, placebo-controlled study. However, the allocation was not computerized. The treatment groups were treated similarly. All study groups were followed-up the same way and the tablets and

packaging looked the same for all 3 groups. Patients were taking the medication the same way regardless of their group (i.e. twice a day from the 15-24th day of their cycle). Moreover, the authors provided a definition of a PMS diagnosis and the inclusion criteria for the patients. The authors also provided a flow chart of the study design. In this, the reader gained a good understanding on how the study was randomized, allocated, followed-up, and analyzed.

Patient demographic information was not included. The readers were not provided information about patient specific characteristics and risk factors such as ethnicity, smoking status, supplement intake, average time spent outdoors, and exercise routine. The only patient specific information that was provided was average weight, age, and age of menarche. The study had a small sample size- only 160 participants were included. 14 participants dropped out of the study and the researchers didn't include these participants in their analyses. As such, intention to treat analyses was not followed and the results can cause an attrition bias. The results from the study concluded that calcium+ vitamin D improved the severity of symptoms of PMS but readers don't know if it was because of the combination of the 2 products or whether one product is better than the other. Another disadvantage for this study was that the researchers didn't mention that the results were controlled for variables such as sun exposure or calorie intake of vitamin D. Moreover, the exact P values were not given. The researchers either put "<0.05" or ">0.05". As such the readers don't know how significant the results are. The follow-up period for the treatment phase for this study was 2 months, which may not have been a long enough time to assess if PMS symptoms have been reduced. Lastly, the participants for this study were all students from the Shiraz University. As such, it is difficult to apply the results of the study to the general population, as all the participants were very similar.

Critical Appraisal Conclusion: After critically appraising the article, many disadvantages were found. Even though this was a double-blinded placebo controlled randomized study, the results are questionable because the numbers were not controlled for variables (i.e. age and calorie intake) and the exact P values were not given. The only conclusion that can be made from this study is that calcium plus vitamin D and dydrogesterone may reduce the severity of PMS symptoms. Further research needs to be completed to determine if vitamin D reduces the symptoms of PMS.

Primary Literature: Article #3

Bertone-Johnson ER, Hankinson SE, Bendich A, Johnson SR, Willett WC, Manson JE. Calcium and vitamin D intake and risk of incident premenstrual syndrome. Arch Intern Med. 2005 165:1246-1252[3]

Study Objectives

To determine the relationship between calcium and vitamin D intake with the risk of incident of PMS.

Methods

- **Design:**
  - Case control study based off of the prospective Nurses' Health Study II (NHS2) cohort study
    - NHS2 study: cohort of 116, 678 US female registered nurses between 25-42 years of age who answered a mailed questionnaire in 1989 and every subsequent 2 years.
- **Allocation:**
  - N/A
- **Blinding:**
  - N/A
- **Follow-up period:**
  - N/A
- **Setting:**
  - N/A
- **Participants:**
  - Exclusion criteria: cancer diagnosis, endometriosis, irregular menstrual cycles, infertility before their reference year
  - Inclusion criteria: no reports of menopause or hysterectomy
  - Of the 116 678 participants of the NHS2 study, 6000 women between the ages of 27-44 (3,430 women reported a diagnosis for PMS & 2,570 with no reported diagnosis) were asked to fill a questionnaire to determine if they met the definition of having PMS
    - Completed questionnaires were received from 2966 (86.5%) of the women self- reporting PMS and 2504 (97.4%) of the women not reporting PMS
    - 1,057 (35.6%) of the 2966 women who reported PMS were classified as having PMS and 968 (78.6%) of the 2,504 who didn't report PMS were classified as not having PMS

- **Intervention:**
  - Intake of calcium and vitamin D were assessed with the 131-item semi-quantitative food frequency (SFFQ) questionnaire in 1991, 1995, and 1999 and standard biennial NHS2 questionnaires were used in 1993 (calcium) and 1997 (calcium and vitamin D).
  - Other information related to either PMS or calcium and vitamin D intake was collected such as age, smoking, BMI, physical activity, and pregnancy.
- **Patient Follow-up:**
  - N/A

Main Results

- There are 4 categories for which data was given 1) total calcium intake 2) calcium from food 3) total vitamin D intake 4) vitamin D from food
  - Each category has 5 quintiles (quintile 1= lowest intake, quintile 5 =highest intake)
  - 3 of the 20 values had a confidence interval that did not pass through 1
- Women in the highest quintile of total vitamin D intake (median 706 IU/d of vitamin D) had a RR of 0.59 (95% CI: 0.40-0.86) compared with those in the lowest quintile (median 112 IU/d of vitamin D; CI not given)
- Women in the highest quintile of calcium from food sources (median 1283 mg/d calcium) had a RR of 0.70 (95% CI 0.50-0.97) compared with those in the lowest quintile (median 529 mg/d); CI not given

Conclusion

The study found a risk reduction for PMS for total vitamin D intake and calcium from food sources. There was no correlation found with PMS for vitamin D intake from food and total calcium intake.

Critical Appraisal

The article was relatively well done. The sample was not small and the researchers gave details about the participants such as BMI, smoking cessation, and physical activity. The inclusion and exclusion criteria were given and readers were given the criteria for

a PMS diagnosis. Moreover, the statistical analyses section provided many details. For example, all statistical analyses were conducted with SAS statistical software and multivariable analyses were used to adjust for variables such as age, BMI, and smoking status. This article had a case control study design, which is not ideal since randomized, double-blinded, placebo-controlled studies are preferred. All of the participants were nurses and the ethnicity for the participants was not disclosed, therefore it is difficult to generalize the results.

The author's conclusions are very misleading. The confidence interval passed through 1 for the majority of the values. In the abstract the authors highlight the value for the highest quintile for total vitamin D intake and the highest quintile for calcium from food sources. These values represent 2 of the 3 values that had a confidence interval that didn't pass through 1 (17 values = not clinically significant). At first glance, the results look very promising; however, once readers review the confidence interval, the results are very limited.

Critical Appraisal Conclusion: After critically appraising the article, the results are limited because the confidence interval passed through 1 for many of the values. Moreover, the study had a case control design, which is not ideal. However, despite this it can be concluded that total vitamin D intake and calcium intake from food may lower the risk of PMS.

Secondary literature: Article #4 (systematic review)

Murphy PK, Wagner CL. Vitamin D and Mood Disorders Among Women: An integrative review. J Midwifery Women's Health. 2008; 53: 440-446[4]

Study objectives

- Review research studies that have examined the relationship between vitamin D and mood disorders that affect women and determine whether further research needs to be done.

Scope

- 6 research studies evaluating the relationship between vitamin D and mood disorders were reviewed
    - 1 article on SAD, 1 on seasonal mood changes, 1 on PMS, 1 on major depressive disorder, 1 on major depression, and 1 on mood disorders
- 1 of the 6 research articles evaluated PMS:
    - Study design: comparative descriptive
    - Sample: n=46; 28-42 year olds; all white females
    - Measurement instrument: self-recorded diary of PMS related symptoms
    - Key findings: PMS group has significantly lower $25(OH)D_3$ levels than controls (19.5+/- 7.5 vs. 25.3+/- 8.3 ng/ml; $P<0.02$)

Methods

- Literature search using CINAHL, PsycINFO, MEDLINE, and PubMed databases and searching old reference lists from selected articles using the following key words: vitamin D; $25(OH)D_3$; depression; seasonal affective disorder; premenstrual syndrome; postpartum depression; perinatal depression; depressive disorder; mood disorder; and women
- Timeframe: 1971-2008
- Inclusion criteria: sample consisted of at least 50% women, focus was on subjects with major depressive disorder, SAD, PMS, postpartum depression, perinatal depression, or other mood disorders, and if serum $25(OH)D_3$ was measured
- Critiqued using the U.S. Preventive Services Task Force (USPSTF) rating system to evaluate the strength of the research

Main Results

- Limited number of peer-reviewed articles looking at mood disorders and serum $25(OH)D_3$
- Of the 6 studied reviewed, 4 reported significant results showing a relationship between low serum $25(OH)D_3$ and mood disorder; including the PMS study
    - All 4 studies had flaws within the sampling, methodology, or analyses
- The following is the review of the PMS article:
    - Sampling: composed of mostly all white females which limits its generalizability

- Methodology: the assay for which the $25(OH)D_3$ was not disclosed
- Analysis: the article noted that participants who were vitamin D deficient were more likely to experience a mood disorder of varying types vs. participants who were sufficient or insufficient in vitamin D status.
- USPSTF rating: fair

Conclusions

Even though all of the studies had limitations, the studies showed a significant association between mood disorders and low vitamin D levels. The authors conclude that there is some kind of biochemical mechanism between vitamin D and women mood disorders and further research needs to be done to examine Vitamin D on specific mood disorders such as PMS.

Critical Appraisal

Overall, this was a relatively well-done literature review. The authors included all the relevant information in the design and search methods. However, the authors said that the studies were also found from searching old reference lists from "selected" articles, which is vague. The literature review only looked at 6 articles and of the 6 articles only 1 of the articles was specific to PMS. Therefore the literature review usefulness is limited.

The articles were critiqued using a published rating system: the USPSTF rating system. The criteria for randomized control trials and descriptive studies were included. However, it would have been helpful if the rating scores were included in an appendix so readers could get a comprehensive idea of the strengths and weakness of all the studies.

It was confusing figuring out what the limitations were for each specific article because the review only included general summaries in heading such as "sampling" and "methodology" rather than first criticizing each article and then summarizing. If the reader wants to know the limitations for a particular article, he/she has to first find the superscript in the reference section and then search through the discussion for that number.

Critical Appraisal Conclusion: In conclusion, this literature review has limited usefulness because only 1 article reviewed was specific to PMS. This article was not a randomized trial and has limitation in the sampling, methodology, and analyses. However, despite these limitations, it can be concluded that low Vitamin D may be associated with symptoms of PMS and further research needs

to be done.

Tertiary literature: Reference # 5 (Internet Database)

Natural Medicines Comprehensive Database (NMCD). Vitamin D Monograph. www.naturaldatabase.com. Accessed July/17/2013

Source Description

Natural Medicines Comprehensive database is a database that provides unbiased information on complementary and alternative therapies, continuing education courses, and clinical management series. The database has a large team of pharmacists and doctors as researchers & writers and members of the editorial review board. The database team uses an evidence-based approach, systematically reviews and appraises literature, uses the most up-to-date data, and gives higher quality data more weight compared to lesser quality data. New literature is monitored and reviewed everyday and the database is updated on a daily basis.

Summary

Vitamin D has recently been studied for the prevention of premenstrual syndrome. Currently, there is data that women who have higher intake of vitamin D, whether it's from supplements or food intake, can decrease the risk of getting PMS or lessen the symptoms. Women who consume 706 IU of vitamin D in a day have a 40% lower risk of developing PMS symptoms vs. women with an average vitamin D intake of 112 IU/day.

Comments/ Critical Appraisal

Natural Medicines Comprehensive Database is a reliable source of information. The vitamin D conclusions were part of the clinical management series in the database. 2 recent articles were referenced for the summary and both of the articles have already been discussed in this abstract (primary literature #2 and #3). The information provided in the database was useful because it provides the

reader with an amount of vitamin D i.e. 706IU/day that has been shown to lower the risk of developing PMS symptoms. However, the database does not identify any limitations of the articles.

Secondary/Tertiary Literature # 3

Vitamin D. Natural Standard. Available at: www.naturalstandard.com/databases/vitamind. Accessed: July 10, 2013.

Source description

Natural Standard is a database that provides unbiased information on foods, herbs, & supplements, health & wellness, medical conditions, sports medicine, environment & global health, genomics & proteomics, and animal health. The editorial board consists of many pharmacists and physicians. The monographs that are provided on the databases are developed by healthcare professionals and are reviewed blindly by a multidisciplinary team at major academic centers. The database is updated regularly and topics are searched are renewed every 3-12 months, depending on the topic.

Summary

High intake of calcium and vitamin D may reduce the risk PMS. In a study, women with the highest total daily vitamin D intake (706IU) had a relative risk of 0.59 vs. those with the lowest intake (112IU). Calcium intake was similar in that participants with the highest daily intake (128 mg) had a relative risk of 0.70 compared to those with the lowest (529mg). Further research needs to be completed before calcium and vitamin D can be recommended.

Comments/ Critical Appraisal

Natural Standards is a reliable source of information. The database refers to 1 article in regards to vitamin D and PMS, which has already been discussed in this abstract (primary literature #3). The database does provide some useful information as it gives the reader the relative risk reduction of PMS by taking 706IU/day of vitamin D. However, the database just uses the 1 literature therefore the summary is not very thorough as there are more published articles available that could have been reviewed. Moreover, the database does not provide the reader with the limitations of the study. The only conclusion the reader can draw from the database is that the intake of Vitamin D and calcium may be associated with a lower risk of developing PMS.