VITAMIN D AND DEPRESSIVE SYMPTOMS IN WOMEN DURING THE WINTER:

A PILOT STUDY

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To the Faculty of Washington State University:

The members of the Committee appointed to examine the clinical project of CLARISSA SHIPOWICK find it satisfactory and recommend that it be accepted.

[Signatures]

Chair

Rita C. Binder

Robert B. Bandel
ACKNOWLEDGEMENTS

To Blue Mountain Medical Group, Dr. Moore and his staff for taking the extra time to conduct this study.

To Robert Bendall for contributing your statistical expertise.

To my chair, Cindy Corbett for your all your hard work, revisions and contributions to the excellence of this clinical project.

To Ruth Bindler for never hesitating to believe in this study and for enhancing the quality of this final paper.
DEDICATION

To the Creator of the human body for giving us the ability to take ordinary sunlight and transform it into an extraordinary hormone that regulates bone health, fights disease and elevates mood.

To my brother David and his wife Madeline and their heroic fight against ovarian cancer which ended on June 29, 2007. In the hope that continued vitamin D research may lead to prevention and a cure.

To my sister, Mary for all your expertise and for believing in me and this research despite the daunting obstacles.

To my brother Clinton, who instilled in me the work ethic that has kept me achieving.

To my mother, for never being afraid to get a little sun.
Abstract

Background: More than half of all women do not meet daily vitamin D nutrient intake recommendations, and research indicates that vitamin D supplementation during the winter may decrease depressive symptoms.

Objectives: To examine the relationship of vitamin D supplementation and depressive symptoms in women living in a northern climate during the winter months.

Method: In a quasi-experimental pilot study, nine women with serum vitamin D levels (as measured by 25 OH vitamin D) below 40 nanograms/milliliter (ng/mL) were administered the Beck Depression Inventory II (BDI-II). After eight weeks of vitamin D₃ supplementation, six of these women completed the BDI-II and had their serum 25 OH vitamin D levels re-assessed.

Results: The baseline and follow-up mean 25 OH vitamin D levels for the sub sample of six women were 21.8 ng/mL (SD = 8.33, range = 14-37) and 48.2 (SD=20.01, range 29-84) respectively (t = -4.11, p = .009). The baseline and follow-up mean BDI-II scores were 31.8 (SD = 4.79, range = 26-40) and 21.2 (SD = 11.07, range = 8-37) respectively (t = 3.37, p = .02). Vitamin D supplementation was associated with an increase in the serum D levels by an average of about 27 ng/mL, and was associated with a decline (demonstrating a negative correlation) in the BDI-II scores of an average of about 10 points. Vitamin D levels above 40 ng/mL at the end of the study were associated with BDI-II scores of 14 or less, a level indicative of minimal depressive symptoms.

Discussion: This pilot study suggests that supplemental vitamin D₃ improves serum 25 OH vitamin D levels and reduces depressive symptoms. Adequately powered clinical trials are needed to better evaluate these relationships.

Key Words: depression, women, vitamin D
Vitamin D and Depressive Symptoms in Women During the Winter

Nursing is concerned with the prevention and correction of nutritional deficiencies in order to promote health and prevent disease. It has been hypothesized that low vitamin D levels in the winter account for exacerbation of melancholia (Vasquez, Manso and Cannell, 2004). Vitamin D can be obtained through food consumption or synthesized by the body from sun exposure. For people living in northern climates (above the 37th degree latitude), the oblique angle of the sun’s rays during the autumn and winter precludes vitamin D synthesis and vitamin D deficiency/insufficiency is common (Rucker, Allen, Fick & Hanley, 2002). In addition, food consumption data suggests that the intake of vitamin D is below current recommendations for more than 50% of women (Institute of Medicine, Food and Nutrition Board, 1999). Thus, women who live above the 37th degree latitude may be particularly at risk for low vitamin D levels during the autumn and winter months.

The National Academies of Science (2004) recommends the following dietary intake of vitamin D: 1 to 50 years of age, 200 International Units (IU); 51 to 71 years of age, 400 IU; over 71 years of age, 600 IU. Many experts believe that these values are too low to support maximal nutritional health and are low in comparison to the amount of vitamin D made endogenously from sun exposure (10,000 to 20,000 IU vitamin D within 24 hours of exposure) (Hollis, 2005).

Vitamin D deficiency is defined as serum levels below 20 nanograms per milliliter ng/mL). A nanogram is one-billionth of a gram (Pickett, 2000). Serum 25 OH vitamin D is a reflection of the metabolite of vitamin D2 and vitamin D3 and is the preferred method of assessing the nutritional adequacy of vitamin D (Jacobs, Oxley & DeMott, 2001). Vitamin D insufficiency is defined as serum 25 OH levels greater than 20 but less than 40 ng/mL. Optimal 25 OH vitamin D levels are defined as between 40 and 65 ng/mL and vitamin D excess is
defined as levels greater than 80 ng/mL (Vasquez, Manso & Cannell, 2004). Toxic levels do not occur until circulating levels are over 125 ng/mL (Holick, 2003).

Low levels of vitamin D have been hypothesized to contribute to depressive symptoms (Vasquez, Manso and Cannell, 2004). Research shows that women are more susceptible to depression than men (Kornstein & Sloan, 2003). Women under forty years of age are four times more likely to have seasonal affective disorder than men (Gaines, 2005). In the United States alone, “the direct and indirect costs of depression are estimated at $60 billion a year” (Kahn et al., 2004, p.346). According to the World Health Organization (WHO), by the year 2020 depression will be the leading cause of disability worldwide (WHO, 2000). In the health care setting, hypertension is the only condition that is seen more frequently (Whooley & Simon, 2000). Thus, vitamin D supplementation may provide a natural remedy for seasonal mood fluctuations.

Data from various studies demonstrate that vitamin D deficiency/insufficiency is common in populations inhabiting northern latitudes especially during the winter months (Jorde, Waterloo, Haug & Stuartberg, 2005; Lansdowne & Provost, 1997; Rucker, Allen, Fick & Hanley, 2002; Gloth, Alum & Hollis, 1999; Vieth, Kimball, Hu & Walfish, 2004). Furthermore, studies indicate that vitamin D supplementation (400 IU to 10,000 IU) and subsequent increased vitamin D levels are associated with reduced depressive symptoms (Brown, Goldstein-Shirley, Robinson & Casey, 2001; Jorde, Waterloo, Haug & Stuartberg, 2005; Lansdowne & Provost, 1997). Thus, vitamin D supplementation may provide a natural, inexpensive, and accessible remedy for seasonal mood fluctuations.
Purpose of the Study

The purpose of this study was to identify the association between vitamin D supplementation and depressive symptoms of women with low serum 25 OH vitamin D levels during the winter months. The following research questions guided the study: 1) Is there a significant relationship between vitamin D levels and depressive symptoms? 2) Do depressive symptoms in women with low serum 25 OH vitamin D levels improve eight weeks after initiation of vitamin D3 supplementation (5,000 international units (IU) daily) during the fall and winter?

Conceptual Model

Vitamin D3 is hydroxylated in the liver to become 25 OH vitamin D, the major circulating form of vitamin D. It is activated in the kidneys to become the hormone 1,25 OH vitamin D where it is tightly regulated (Holick, 2003). Both unactivated and activated vitamin D can cross the blood brain barrier (Kiraly, Kiraly, Hawe & Makhani, 2006). Recent research has shown that organs like the brain can activate 25 OH vitamin D, use it within their own cells and extinguish it (Holick & Jenkins, 2003). Based on this data, a bio-psychological framework of vitamin D as a hormone that influences depressive symptoms served as an emerging model (Figure 1). Three physiologic pathways between vitamin D and depressive symptoms were identified. These are vitamin D in its active form in the body has been shown to: 1) stimulate serotonin (Gaines, 2005) a neurotransmitter associated with mood elevation (Stahl, 2000); 2) be associated with down-regulation of glucocorticoid receptor gene activation which is found to be upregulated in depression; and 3) be neuroprotective, shielding neurons from toxins such as glucocorticoids and other excitotoxic insults (Obradovic, Gronemeyer, Lutz & Rein, 2006).
Literature Review

In a randomized quasi-experimental study targeting mild to moderately depressed women (N=112), lifestyle interventions were effective in significantly reducing depressive symptoms (Brown, Goldstein-Shirley, Robinson & Casey, 2001). The three-fold intervention involved moderate intensity walking, increased light exposure and vitamin supplementation, including 400 IUs of vitamin D. The study is important because the participants were women and the interventions were healthy lifestyle changes. One study limitation was the inability to isolate the specific variable or variables affecting the outcome and the degree of effect for each variable or combination of variables.

In another study, healthy undergraduate students (N=44), not taking vitamin supplements during the winter were given either 400 or 800 IU of vitamin D$_3$ for five days (Lansdowne & Provost, 1997). Depressive symptoms, as measured by a self-reported depression inventory, were alleviated with vitamin D, regardless of dose. Limitations of this study included a small sample size and the failure to address differences between males and females. The relationship between vitamin D supplementation and improved mood was significant.

The Tromso study, conducted in northern Norway, measured serum calcium and parathyroid hormone (PTH) in 7,950 participants with the intent of identifying altered calcium or PTH levels. Subsequently, a secondary analysis of 21 participants who had been experiencing secondary hyperparathyroidism (SHPT) without renal failure was conducted. The 21 participants with SHPT from the Tromso study were compared to 63 controls who did not have SHPT. SHPT is usually caused by low levels of vitamin D. The 21 participants with altered calcium metabolism demonstrated neuropsychological problems. A relationship between serum levels of vitamin D and depressive symptoms was also documented. Low serum levels of
vitamin D correlated with a higher Beck Depression Inventory score, identifying a correlation between vitamin D and depressive symptoms (Jorde, Waterloo, Haug & Stuartberg, 2005).

**Methods**

Following university IRB approval and the approval of the clinical agency where the study was carried out, a quasi-experimental pre-test post-test design was applied with women participants acting as their own pre-post control. Female patients (N=9) being treated at a medical clinic in southeastern Washington for vitamin D deficiency/insufficiency voluntarily participated in this study. Initial evaluations took place between December and March. During these months vitamin D stores are typically low and the impact of vitamin D supplementation should be most visible in participants. Exclusion criteria for the study included: 1) those with mental impairments such as dementia or language barriers that may have inhibited answering written questions, 2) women who were using or planned to use tanning beds or other phototherapy, 3) women who planned on traveling to sunnier, more tropical or southern areas (e.g., Mexico, Hawaii, Arizona) during the winter, and 4) women taking or planning to take antidepressants.

**Ethical Considerations**

The study protocol was submitted to the Washington State University (WSU) Institutional Review Board (IRB) for approval. All investigators in this study completed human subjects participation training to assume this role. Written informed consent was obtained from all participants. During the consent process, potential participants were informed that participation or non-participation would not affect any current or future care provided at the clinic. Patients were informed that data would be confidential and the BDI-II scores would be
used for research purposes only. Participants were told that they could refuse to answer questions that made them uncomfortable and could withdraw from the study at anytime.

Data was collected on actual BDI-II questionnaires where participants selected the answer they wished to choose based on a Likert scale. These questionnaires include study identification (ID) numbers and dates. Pre- and post-tests were kept in separate locked file boxes. A file folder with participant names and corresponding study ID numbers was kept in a separate locked file.

**Procedure**

Per usual medical care at the clinic, participants who had fasting blood tests indicating serum 25 OH vitamin D levels below 40 nanograms/milliliter (ng/mL) were advised to initiate vitamin D₃ supplementation (5,000 IU/day) by their physician. At the time of the vitamin D₃ supplementation recommendation, women were informed of the research opportunity. Women agreeing to participate completed the Beck Depression Inventory II (BDI-II) survey prior to initiating vitamin D₃ supplementation. After the eight weeks of D₃ supplementation, participants returned to the clinic to have their serum 25 OH vitamin D level evaluated per usual clinic protocol and once again completed the BDI-II survey. Participants gave permission for their medical records to be accessed to document serum vitamin D levels for the study. Pre and post BDI-II scores and serum 25 OH vitamin D levels were correlated and analyzed for differences. Of the nine participants, six provided BDI-II and serum vitamin D levels 8 weeks after vitamin D₃ supplementation.

**Data Analysis**

SPSS 14.0 (SPSS Inc., 2005) was used to perform statistical analysis. Descriptive statistics were used to screen and clean the data as well as to describe the characteristics of women participating in the study. Participants who did not complete the post-supplement
measurements were not included in the correlational and inferential analyses. Cronbach’s alpha for the BDI-II was .81 at baseline and .95 at follow-up.

Results

Of the nine initial participants in the study, six (n = 6) completed the study. Of the six, five were married and one was single. The subsample of six women who completed the study had a mean age of 42.2 years (SD = 13.17, range = 23-55). Their baseline and follow-up mean vitamin D₃ levels were 21.8 (SD = 8.33, range = 14-37) and 48.2 (SD=20.01, range 29-84) respectively (t = -4.11, P = .009). The baseline and follow-up mean BDI-II scores were 31.8 (SD = 4.79, range = 26-40) and 21.2 (SD = 11.07, range = 8-37) respectively (t = 3.37, p = .02) (Table 1). For completeness, the Wilcoxon signed rank test was also computed and showed significance for both BDI-II scores (p = .028) and vitamin D levels (p = .027). The correlation between BDI-II and vitamin D levels was insignificant (r =.154, p =.77) at baseline; although it increased in magnitude at follow-up (r = -.623) it remained statistically insignificant (p = .19) (Table 2). The bivariate correlation between baseline and post-supplement BDI-II scores was .804 and between vitamin D levels was .672, but these correlations were statistically insignificant (p = .186). Normal vitamin D levels (>40 ng/mL) were achieved after supplementation for only three participants (Figure 2). These same three participants had BDI-II scores after supplementation of 14 or below (Figure 3).

Discussion

Results indicate that vitamin D supplementation during the fall and winter months in women with low serum 25 OH vitamin D levels is associated with increases in serum 25 OH vitamin D and reductions in depressive symptoms. Following supplementation, serum vitamin D increased in all participants with an average increase of 27 ng/mL. While this study consisted of
a small sample, it suggests supplementation, particularly if provided at high enough levels to achieve normal serum 25 OH vitamin D levels may be clinically significant. At the prescribed supplemental intake of 5,000 IU daily, only half the women in this study achieved a serum 25 OH vitamin D level over 40 ng/mL. However, a significant reduction in depressive symptoms was realized after supplementation. Further, among the three women with an ending vitamin D level over 40, all had BDI-II scores of 14 or less, indicating minimal depressive symptoms. These three women had pre-supplement BDI-II scores that ranged from 26-31 with a mean of 28.67 ng/mL. In summary, this pilot study provides preliminary evidence to suggest that women who suffer from seasonal depressive symptoms may benefit from vitamin D₃ supplementation if serum levels of 25 OH vitamin D are low (< 40 ng/mL). Further research with a larger sample size and stronger design is warranted to continue to investigate the clinical utility of vitamin D₃ supplementation.

Limitations

The small convenience sample participating in this pilot study limits the ability to generalize the results. Replication of this study with a larger, adequately powered sample is needed to provide a more definitive understanding of the relationship between vitamin D supplementation and seasonal depressive symptoms.

Additionally, further research to determine factors related to vitamin D₃ dosing is needed. The reason(s) for three of the women not achieving serum vitamin D levels above 40 ng/mL is unclear. It may be that these women were not consistently taking the vitamin D₃, that they required longer than eight weeks of supplementation to achieve optimal vitamin D levels or that a higher vitamin D₃ dose was needed to achieve optimal vitamin D levels. More frequent analyses of serum 25 OH D levels and measuring adherence to supplementation are warranted in
future studies. Future studies should be conducted with a randomized and blinded design to account for placebo effects.

**Significance to Nursing**

Nursing is concerned with proper nutrition to promote health and prevent disease. This study examined the relationship between vitamin D$_3$ supplementation in women with low serum 25 OH vitamin D levels and depressive symptoms. The findings of this pilot study suggest that supplemental vitamin D$_3$ intake may be a nutritional approach that can help augment other treatments. If further research upholds the efficacy of vitamin D$_3$ supplementation in relieving depressive symptoms, nurses can use this information to instruct their clients regarding supplementation with vitamin D$_3$. 


References


Table 1.
PAIRED SAMPLES STATISTICS AND TESTS

Paired Samples Statistics (n = 6)

<table>
<thead>
<tr>
<th>Paired Samples</th>
<th>Mean</th>
<th>Mean Diff.</th>
<th>Std. Deviation</th>
<th>Avg. Std. Deviation</th>
<th>t</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>BDI-II(1)</td>
<td>31.833</td>
<td>10.6667</td>
<td>4.79236</td>
<td>7.7616</td>
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<td>.020</td>
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<tr>
<td>BDI-II(2)</td>
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<td></td>
<td>11.07098</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-OH-D(2)</td>
<td>48.166</td>
<td></td>
<td>20.01416</td>
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Table 2.
PAIRED SAMPLES CORRELATIONS

<table>
<thead>
<tr>
<th>Paired Sample</th>
<th>N</th>
<th>Correlation (r)</th>
<th>Sig.(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pair 1 BDI-II (1) &amp; BDI-II (2)</td>
<td>6</td>
<td>.804</td>
<td>.054</td>
</tr>
<tr>
<td>Pair 2 25-OH-D (1) &amp; 25-OH-D (2)</td>
<td>6</td>
<td>.672</td>
<td>.144</td>
</tr>
<tr>
<td>Pair 3 BDI-II (1) &amp; 25-OH-D (1)</td>
<td>6</td>
<td>.154</td>
<td>.770</td>
</tr>
<tr>
<td>Pair 4 BDI-II (2) &amp; 25-OH-D (2)</td>
<td>6</td>
<td>-.623</td>
<td>.186</td>
</tr>
</tbody>
</table>
Figure 1: The Bio-psychological Model of Vitamin D: Hormone that Elevates Mood

- Oral Vitamin D₃ Supplementation
- LIVER
  - 25(OH) D
  - 1,25(OH)D
  - Activated Vitamin D (1,25(OH)D)
  - Increases Serotonin
  - Protects Neurons from Toxins
  - Decreases Glucocorticoid Receptors
- KIDNEYS
- THE BLOOD
- BRAIN
- BARRIER

Adapted from Figure 1.3 New understanding of how vitamin D benefits health (Holick & Jenkins, 2003).
This graph shows that vitamin D₃ supplementation is associated with an increase in serum 25 OH vitamin D levels by an average of 27 ng/mL after eight weeks.
This graph shows that vitamin D supplementation is associated with a decline (improved mood: a negative correlation) in BDI-II scores of an average of about 10 points.
MEMORANDUM

TO: Clarissa Shipowick, C. Barton Moore and Dr. Varnell Nursing, WSU, Walla Walla
FROM: Malathi Jandhyala (for) Kris Miller, Chair, WSU Institutional Review Board
DATE: 25 January 2007
SUBJECT: Review of Protocol Modification - Modification

Your proposal to modify the protocol titled "Vitamin D and Depression in Women," IRB File Number 9453-c was reviewed for the protection of the subjects participating in the study. Based on the information received from you, the IRB has approved your modification request on 25 January 2007. This modification includes editorial changes to the letter to potential participants who are patients in the clinic to inform them of the study.

IRB approval indicates that the modifications described to the previously approved study protocol are designed to adequately protect the subjects participating in the study. This approval does not relieve the investigator from the responsibility of providing continuing attention to ethical considerations involved in the utilization of subjects participating in the study.

The approval for this protocol expires 20 December 2007. If any more changes are made to the study protocol you must notify the IRB and receive approval before implementation.

If you have questions, please contact the Institutional Review Board at OGRD (509) 335-9661. Any revised materials can be mailed to Office of Research Assurances (Campus Zip 3140), faxed to (509) 335-1676, or in some cases by electronic mail, to irb@wsu.edu.

Review Type: MOD OGRD No.: NF
Review Category: XMT Agency: NA
Date Received: 25 January 2007
Clarissa Shipowick

From: "Holick, Michael F" <mfholick@bu.edu>
To: "Clarissa Shipowick" <cvshipowick@charter.net>
Sent: Tuesday, July 17, 2007 7:37 AM
Subject: RE: Vitamin D Model

The adapted version is fine and you have my permission to use it.
Best, Michael

--- Original Message ---
From: Clarissa Shipowick [mailto:cvshipowick@charter.net]
Sent: Tuesday, July 17, 2007 10:00 AM
To: Holick, Michael F
Subject: Re: Vitamin D Model

Dr. Holick,
Can you write me an e-mail granting permission to use my adapted version of vitamin D in my clinical project? I do realize that the brain can take unactivated vitamin D and activate it. This is a fascinating breakthrough.
Thank you.
Clarissa Shipowick

From: Holick, Michael F
To: Clarissa Shipowick
Sent: Tuesday, July 17, 2007 12:41 AM
Subject: RE: Vitamin D Model

Also 25(OH)D may be converted to 1,25(OH)2D in the brain.
Good luck. Here is a review that might be useful that will be out this week.
Best, Michael

From: Clarissa Shipowick [mailto:cvshipowick@charter.net]
Sent: Tuesday, July 17, 2007 2:09 AM
To: Holick, Michael F
Cc: Cindy Corbett
Subject: Vitamin D Model

Dr. Holick,
I am getting my masters degree in Nursing from Washington State University. My clinical project is entitled "Vitamin D and depressive symptoms in women during the winter months". Can you give me permission to use this adapted model for my clinical project at Washington State University? Please see my model in the attachment.
Thank you.
Clarissa Shipowick
MEMORANDUM

TO: Clarissa Shipowick and C. Barton Moore  
Nursing, WSU, Walla Walla

FROM: Malathi Jandhyala (for) Kris Miller, Chair, WSU Institutional Review Board (3140)

DATE: 21 December 2006

SUBJECT: Approved Human Subjects Protocol - New Protocol

Your Human Subjects Review Summary Form and additional information provided for the proposal titled "Vitamin D and Depression in Women," IRB File Number 9453-a was reviewed for the protection of the subjects participating in the study. Based on the information received from you, the WSU-IRB approved your human subjects protocol on 21 December 2006.

IRB approval indicates that the study protocol as presented in the Human Subjects Form by the investigator, is designed to adequately protect the subjects participating in the study. This approval does not relieve the investigator from the responsibility of providing continuing attention to ethical considerations involved in the utilization of human subjects participating in the study.

This approval expires on 20 December 2007. If any significant changes are made to the study protocol you must notify the IRB before implementation. Request for modification forms are available online at http://www.ogrd.wsu.edu/Forms.asp.

In accordance with federal regulations, this approval letter and a copy of the approved protocol must be kept with any copies of signed consent forms by the principal investigator for THREE years after completion of the project.

Washington State University is covered under Human Subjects Assurance Number FWA00002946 which is on file with the Office for Human Research Protections.

If you have questions, please contact the Institutional Review Board at (509) 335-9661. Any revised materials can be mailed to the Office of Research Assurances (Campus Zip 3140), faxed to (509) 335-1676, or in some cases by electronic mail, to irb@wsu.edu.

Review Type: NEW          OGRD No.: NF
Review Category: EXP         Agency: NA
Date Received: 29 November 2006