Vitamin D Supplementation as an Adjunct Therapy to Improve Physical Function and Decrease BNP in Adults with Congestive Heart Failure

Mary Titmus

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Abstract

Background: Congestive heart failure (CHF) is a highly prevalent condition among aging adults, and a common cause of hospitalization in the United States. It is consequently a great financial burden. Many studies have shown a correlation between vitamin D deficiency and CHF, but little is known about the benefits, if any, of vitamin D supplementation in adults with CHF.

Methods: An exhaustive search was conducted using Medline-OVID, Medline-PubMed, and Web of Science using the keywords: vitamin D supplementation and heart failure. Relevant articles were assessed for quality using GRADE.

Results: Three trials were identified as meeting the inclusion criteria. The design of each study varied, as did the results. Two studies evaluated the 6-minute walk test (6MWT) as a measure of physical function. One study showed improvement with treatment and the other showed no change. All three studies measured brain natriuretic peptide (BNP), a hormone released by the heart when it is under stress and a common marker of severity of heart failure. Two studies found a significant decrease in BNP with treatment, and one study found no change.

Conclusion: There is some evidence to suggest that vitamin D supplementation is beneficial earlier in the disease process of CHF, but no evidence at this time to support that it is helpful in more elderly, advanced disease patients. A larger randomized control trial is necessary to provide more evidence for or against vitamin D supplementation in CHF.

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First Advisor
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Vitamin D Supplementation as an Adjunct Therapy to Improve Physical Function and Decrease BNP in Adults with Congestive Heart Failure

Mary Titmus

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies
Pacific University
Hillsboro, OR
For the Masters of Science Degree, August 8th, 2015

Faculty Advisor: Saje Davis-Risen, PA-C
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Mary Titmus is a native of Utah where she majored in Exercise Science at Brigham Young University. After completion of her undergraduate degree, she worked as a phlebotomist and medical supervisor at a blood plasma donation center. She enjoys traveling and participated in a medical outreach program in Nicaragua through Pacific University during her first year in the Physician Assistant program. She is interested in cardiology and inpatient medicine.
Abstract

**Background:** Congestive heart failure (CHF) is a highly prevalent condition among aging adults, and a common cause of hospitalization in the United States. It is consequently a great financial burden. Many studies have shown a correlation between vitamin D deficiency and CHF, but little is known about the benefits, if any, of vitamin D supplementation in adults with CHF.

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**Keywords:** Vitamin D supplementation, Heart Failure
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List of Abbreviations

CHF..............................................................Congestive Heart Failure
NYHA............................................................New York Heart Association
BNP..............................................................Brain Natriuretic Peptide
6MWT............................................................6-Minute Walk Test
IU.................................................................International Units
25 (OH) D.......................................................25 Hydroxyvitamin D
Vitamin D Supplementation as an Adjunct Therapy to Improve Physical Function and Decrease BNP in Adults with Congestive Heart Failure

BACKGROUND

Congestive heart failure (CHF) is a highly prevalent disease and a common cause of hospitalization of adults in the United States. It is a disease causing both morbidity and mortality in elderly patients. Heart failure is often debilitating, and CHF patients experience both a decrease in heart function and physical function as the disease progresses. Increased filling pressures put extra stress on the heart, causing the heart muscle to hypertrophy and eventually stretch. This leads to a decline in the heart’s ability to contract, relax, or both. The result is a back up of fluid into the pulmonary vasculature which leaks into the lungs, causing shortness of breath, especially when the patient lies flat. Fluid can also accumulate in the periphery as the systemic circulation is unable to flow well into the dysfunctional heart. Patients often require frequent follow up with their primary care providers to adjust medical therapy as heart failure progresses. These patients also are frequently admitted to the hospital due to CHF exacerbations, and can require several days of inpatient care to be medically controlled. As such, it is a significant financial burden.

Multiple studies have shown that vitamin D deficiency is common in CHF patients, but there is still uncertainty as to the full effects of vitamin D supplementation on CHF.\(^1,2\) Researchers are still unsure as to the cause of this deficiency, whether it is the result of CHF or a possible contributor to the disease. Vitamin D deficiency is a predictor of mortality in patients with heart failure, and supplementation of vitamin D is associated with decreased mortality.\(^2\)
Vitamin D is a cheap, readily accessible, and safe supplement. It would provide a simple option for adjunct therapy if found to be of benefit in CHF patients. Any potential treatment for CHF would have to show benefits in physical function, cardiac function, or both. A good marker of physical function is the 6-minute walk test (6MWT), which measures how many meters a patient can walk on a flat surface in 6 minutes. Cardiac function is often trended by measuring brain natriuretic peptide (BNP), a hormone released from the walls of the heart when it is stretched and under stress. Levels of this hormone will increase in patients with worsening CHF. Both of these tests quantify changes in CHF. Any therapy showing improvement in the disease process of CHF would potentially equate to slowed disease progression, increased cardiac and physical function, and fewer hospitalizations. With this possibility in mind, analyzing whether vitamin D supplementation can improve function in adults with CHF is an important research question.

**METHODS**

An exhaustive literature search of Medline-OVID, Medline-PubMed, and Web of Science using the terms “vitamin D supplementation” and “heart failure” was undertaken. Preliminary search results were then limited to clinical trials, English language only, and human subjects. Studies were eligible for inclusion if they evaluated adult patients with a current diagnosis of CHF, treated patients with oral vitamin D supplementation for a minimum of 12 weeks, and measured BNP levels, the 6MWT, or both as outcomes. One study was excluded due to a short duration of therapy and follow up. Relevant articles were assessed for quality using GRADE.³

**RESULTS**

The search of literature resulted in three trials addressing the question and meeting inclusion criteria. These studies focused on several different aspects of CHF and used various
markers of disease, but all three studies\textsuperscript{4,5,6} measured brain natriuretic peptide (BNP) and two of the studies\textsuperscript{4,6} measured the 6-minute walk test (6MWT) in patients. All three studies\textsuperscript{4,5,6} looked at adults, although the age range of each study varied considerably. See Table I.

**Amin et al**

This study\textsuperscript{4} examined 100 consecutive patients with the diagnosis of CHF presenting to the Heart Failure and Transplant Clinic of Rajaei Cardiovascular, Medical and Research Center, in Tehran, Iran. Patients were recruited in September 2010 and February 2012, and were all required to be at least 15 years old to be included in the trial. The study consisted of 73 men and 27 women, with an average age of 45.25±15.53 years. All patients were on optimal medical treatment for heart failure according to the latest guidelines for medical management, for at least 3 months prior to the study, and remained on the same medical regimen during the duration of the study.\textsuperscript{4}

Patients were assessed at baseline for NYHA functional class as determined by the same investigator while observing the patient perform activities of daily living. Baseline NYHA class evaluation yielded 3\% of patients in class I, 45\% of patients in class II, and 52\% of patients in class III. The 6MWT, proBNP, and serum 25 (OH) D levels were all collected at baseline, as well as echocardiographic data. Patients were categorized into normal, insufficient, and deficient groups based on vitamin D levels, with 25 (OH) D levels of >30 ng/ml, 20-29.9 ng/ml, and <20 ng/ml respectively. Patients with insufficient or deficient levels were given oral vitamin D3 for 4 months. This was administered at a dose of 50 000 IU every week for 8 weeks, then 50 000 IU every month for 2 months. All patients were evaluated again at the completion of treatment.\textsuperscript{4}
At baseline, 25 (OH) D levels had no statistically significant correlation with NYHA functional class, proBNP, or 6MWT. However, NYHA class was significantly associated with 6MWT, and with proBNP level. After 12 weeks of supplementation, the mean 25 (OH) D level increased by 41.86 ng/ml for a mean of 54.49±18.01 ng/ml (P<.001). NYHA functional class improved significantly (P<.001), as did the 6MWT (P<.001). There was also a significant drop in proBNP hormone levels by 827.32 pg/ml (P<.001). See Table II. This data could not be compared to the untreated group with sufficient 25 (OH) D levels at baseline, as this group only had 6 subjects and was too small for a quality comparison.4

The authors noted that their study was successful in raising the average concentration of vitamin D in their patients to the optimum level. They also recognized that they included a younger population in their study, and that this may contribute to the significant improvement seen in their patients as intervention earlier in the disease process may be more beneficial. They also noted that they used vitamin D3, which has a longer half-life and results in greater peak levels of vitamin D compared to other oral forms of the vitamin. There were no losses due to follow up. However, the authors also acknowledged that their study had a small sample size and had no placebo control group to offer comparison.4

Schleithoff et al

This double-blind, randomized, placebo-controlled trial5 evaluated 123 CHF patients from the Heart and Diabetes Center Nordrhein-Westfalen, Germany. Patients (102 men and 21 women) were recruited between March 2002 and April 2003. Most patients were in their 50s or early 60s, and all participants had a NYHA functional class of II or higher.5
Patients were randomly assigned in a double-blind manner by a computer generated random number list to the intervention group or the control group. The 61 patients in the intervention group were given 2000 IU of vitamin D3 daily, and the 62 patients in the control group were given a placebo daily. Both groups were given 500 mg of calcium daily to ensure patients received the recommended intake for calcium. Therapy lasted for a period of nine months. Baseline levels of proBNP were measured along with other biochemical markers and hemodynamic variables. Patient compliance was documented with bottle counts at each visit. Patients also completed a validated food record the day before each visit to estimate dietary intake of vitamin D and calcium. Thirty patients did not complete the study, 25 of them due to a marked worsening of their health, and the others were excluded due to noncompliance.5

There was no statistical difference between the groups at baseline with the exception of lower interleukin-10 serum levels in the treatment group. After therapy was completed, all measurements were repeated. Vitamin D supplementation increased median 25 (OH) D levels by 26.8 ng/ml for a median of 42 ng/ml (P=.001). There was no significant change in proBNP with vitamin D supplementation. See Table III.5

The authors acknowledged that the increase in serum 25 (OH) D levels in the treatment group was likely below optimal levels, and that higher doses of supplementation resulting in higher serum vitamin D levels would probably result in additional improvement in CHF patients. The authors also noted that there was a relatively high dropout rate in their study. They also recognized that calcium supplementation in both groups may have contributed to changes in cardiac function, but they pointed out that dietary calcium intake in their patients was below the
recommended level, and so recommended calcium levels were only achieved with the supplementation provided by the study.5

Witham et al

This double-blinded, randomized control trial6 evaluated patients age 70 or older with a clinical diagnosis of heart failure, NYHA class II or III. All participants were required to have a 25 (OH) D level <20 ng/ml to be included. Patients were recruited from primary and secondary care clinics in areas of Scotland from June 2005 to October 2008. All patients were of white European origin. A total of 105 patients passed screening to participate in the study.6

Patients were randomized by a computer into the intervention group (53 patients) or the control group (52 patients) and allocation was concealed from all parties. Baseline measurements, including the 6MWT and BNP were recorded prior to any intervention. The treatment group received 100 000 IU of vitamin D2 at this baseline visit, and again at 10 weeks. The control group received a placebo at both of these visits. Administration of each dose was supervised to ensure compliance. Outcomes were then measured again at 10 weeks and 20 weeks. During the trial, a total of 9 patients were lost to follow up due to death, illness, protocol violation, and moving away. There were 48 patients in each group at the end of the study.6

The groups were statistically different at baseline, so the difference in change in outcomes at 20 weeks was adjusted for baseline variables. If data was missing for the 6MWT, it was assumed that the patient could not walk and therefore had a 6MWT result of 0. Failure to perform the 6MWT was due to death, illness, or poor health preventing the patient from being able to stand and walk without assistance. In the treatment group, the increase in 25 (OH) D levels was statistically significant (P<.001) but the mean level at 10 weeks and 20 weeks never
rose above 30 ng/ml. There was no statistically significant change in the 6MWT between the two
groups. However, BNP decreased significantly in the treatment group compared with the control
group by 10 weeks (P=0.04) and continued to drop by 20 weeks (P=0.05). See Table IV.6

The authors of this study acknowledged that there were specific strengths and weaknesses
in this trial. There were narrow confidence intervals around the change in the 6MWT, making it
unlikely that a clinically significant effect was missed. But a major limitation of this study is that
it used vitamin D2 and not vitamin D3 for oral supplementation. Vitamin D3 has a longer half-
life and results in greater peak levels of vitamin D, making it the preferred oral vitamin D
supplementation. However, only vitamin D2 was available at the time of this study. The authors
also note that higher or more frequent doses of vitamin D may be required to see benefits in CHF
patients, and intervention earlier in the disease process may also result in greater effects.6

**DISCUSSION**

Oral vitamin D is a cheap, safe, and well tolerated supplement. Some studies report that
up to 50% of the US population is vitamin D deficient.7 This deficiency is even more common
among CHF patients.8 Because of this, the threshold for recommending this supplement to
patients is likely very low for most clinicians. The Amin et al study4 seems to indicate that
vitamin D supplementation is likely of benefit in younger CHF patients that are early in disease
progression. However, the dosing must be sufficient to raise serum vitamin D levels to an
optimal level, 30 ng/ml or higher, and the treatment likely needs to be weekly or more frequent
dosing and long term.4,5,6 Moreover, vitamin D3 supplementation is preferable over vitamin D2
based on a meta-analysis that concluded such.9 Vitamin D supplementation appears to be less
effective in elderly CHF patients, but until there are more studies evaluating the effects of vitamin D3 supplementation long term there is insufficient evidence to be sure.

Each of these studies had limitations. All of the studies had a small sample size around 100 patients. Amin et al\textsuperscript{4} lacked a placebo treated control group, and therefore had no comparison for the intervention group. This raises the concern that there may be confounding variables affecting the results that the authors did not recognize due to this lack of comparison. Schleithoff et al\textsuperscript{5} and Witham et al\textsuperscript{6} patients had suboptimal vitamin D levels at the end of the study. As a result, the effects of optimal vitamin D levels in these patients are unknown, and there may have been additional benefits with high levels of vitamin D. Witham et al\textsuperscript{6} had the significant limitation of using vitamin D2 instead of vitamin D3, which is considered to be the more beneficial oral vitamin D supplementation. The supplementation was given in two large bolus doses, whereas a more frequent and consistent dosing of vitamin D would likely be more beneficial than an intermittent bolus.\textsuperscript{10} This study also excluded heart failure patients with preserved systolic function, a characteristic common in many heart failure patients.\textsuperscript{11} This prevents the results from being applied to certain types of CHF patients. It should also be noted that this study used a more elderly CHF population, but intervention at a younger age would likely prove to be of greater benefit.

The assumption is that the earlier the intervention and the more frequent the dosing of vitamin D, the more likely the patient will experience the benefits of supplementation. Vitamin D has numerous known health benefits, such as improvement in cognition\textsuperscript{12}, liver disease\textsuperscript{13}, and
bone health.\textsuperscript{14} It also has tremendous potential in improving CHF via various biochemical markers such as parathyroid hormone, tumor necrosis factor, and interleukin-10.\textsuperscript{5}

Based on these results, the overall quality of evidence is very low and future research conducted should include a larger, randomized, double blinded placebo controlled trial using vitamin D3 supplementation in younger CHF patients. It would be imperative to use high, frequent doses of vitamin D3 to ensure optimal levels of serum 25 (OH) D after intervention. Using 6MWT as a measure of physical function, and BNP as a measure of cardiac function would also be recommended. This would provide more conclusive evidence as to whether or not vitamin D supplementation can improve physical function and cardiac function in CHF.

**CONCLUSION**

Research on vitamin D supplementation in CHF patients is still inconclusive. There is some evidence that vitamin D3 is of benefit in younger patients with CHF, but it should be supplemented at an adequate dose to meet optimal levels for the patient to experience benefits. There is currently no evidence that is it helpful in elderly CHF patients, but there is a lack of definitive research for or against supplementing in this population at this time. However, the lack of research does not mean that there is no use for supplementation in these patients, and there is still great potential for improvement of cardiac function and hemodynamic variables in this population. There is a great need for a larger randomized control trial to better evaluate the benefits, if any, of vitamin D3 supplementation in CHF patients.
References


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<th>Indirectness</th>
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\textsuperscript{a}Lack of allocation concealment, lack of blinding and no control group
\textsuperscript{b}Small sample size
\textsuperscript{c}Significant loss to follow up
\textsuperscript{d}Intervention different from available evidence
\textsuperscript{e}BNP is not the primary outcome in this study
### Table II. Amin et al\textsuperscript{4}

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<td>6MWT (m)</td>
<td>363±77</td>
<td>394±61</td>
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<td>proBNP (pg/ml)</td>
<td>2508.60±1867.99</td>
<td>1125.16±696.62</td>
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<td>25 (OH) D (ng/ml)</td>
<td>12.63±7.60</td>
<td>41.33±15.95</td>
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*Mean±Standard Deviation

\textsuperscript{b}P value unavailable due to small control group

### Table III. Schleithoff et al\textsuperscript{5}

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<td>Intervention (n=42)</td>
<td>Control (n=51)</td>
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<td>proBNP (pg/ml)</td>
<td>721 (444,1140)</td>
<td>859 (180,1869)</td>
</tr>
<tr>
<td>25 (OH) D (ng/ml)</td>
<td>14.4 (11.5, 22.1)</td>
<td>15.3 (12.7, 22.8)</td>
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*Median (Interquartile ranges)

### Table IV. Witham et al\textsuperscript{6}

<table>
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<td>Treatment (n=53)</td>
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<td>6MWT (m)\textsuperscript{a}</td>
<td>249±116</td>
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<td>BNP (pg/ml)\textsuperscript{a}</td>
<td>142 (290)</td>
<td>168 (274)</td>
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<td>8.21±3.57</td>
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*Mean±Standard Deviation

\textsuperscript{a}Median (Interquartile Range)