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### Vitamin D Supplementation: Preventing Fractures

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**Vitamin D Supplementation: Preventing Musculoskeletal Fractures**

Michael Doherty and Courtney Carn

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**Abstract:**

**Objective:** To assess the ability of vitamin D supplementation in preventing musculoskeletal fractures. **Methods:** Systematic literature review using Google Scholar search terms “vitamin D supplementation” and “preventing hip fractures” from 2006-2015. Only RCTs, meta-analysis, and clinical guidelines were included. **Results:** Our search resulted in one meta-analysis and two randomized controlled trials. **Conclusion:** The summation of our investigation into vitamin D deficiency and the presence of musculoskeletal fractures has proven to be relatively inconclusive. The resulting data from our three studies did not provide any definitive proof that improved vitamin D levels correlates with better bone health.

**Introduction:**

The current issue surrounding the screening for vitamin D deficiency focuses on a lack of accepted standards for classification and assessment. The United States Preventive Services Task Force (USPSTF), an independent, volunteer panel of national experts on prevention and evidence-based medicine, released a statement in 2014 on its recommendations for vitamin D deficiency screening in adults, stating there was insufficient evidence to assess the efficacy of such screening. Their statement presented multiple industry wide inconsistencies that related to establishing valid vitamin D comparisons. 25 hydroxyvitamin D (calcidiol or 25 OH-D) is the inactivated form of vitamin D that is measured in serum. Various industry constituents classify “deficiency” at different levels - Endocrine Society (<20 ng/mL); Institute of Medicine (<20 ng/mL); National Osteoporosis Foundation (<30 ng/mL); United States Preventative Services Task Force (<30 ng/mL). A lack of continuity creates confusion as to who is deficient and who is not. Testing for 25 (OH)-D has numerous assays such as competitive protein binding, immunoassay, high performance liquid chromatography or combined high performance liquid chromatography and mass spectrometry. Sensitivity and specificity for these tests are unavailable due to lack of a reference standard for comparative analysis. Further variability exists among testing laboratories assay methods and the ranges used per patient sex and ethnicity.<sup>1</sup> There is concern that vitamin D deficiency is associated with increased risk of obtaining fractures and osteoporosis as we age. This

paper aims to explore the efficacy of Vitamin D supplementation for prevention of musculoskeletal fractures.

*Case:* BR is a 55 year old Caucasian female inquiring today about vitamin D supplementation because she heard from a friend that it will help reduce the risk of getting a hip fracture. She has no symptoms and no significant past medical history but has a family history of osteoporosis. Physical examination is unremarkable. Vitamin D screening reveals vitamin D level of 20ng/mL. We are interested to see if supplementation of vitamin D will help reduce her risk of obtaining a hip fracture.

*Patient/Population – Patients over the age 65 years old*

*Intervention – Vitamin D supplementation*

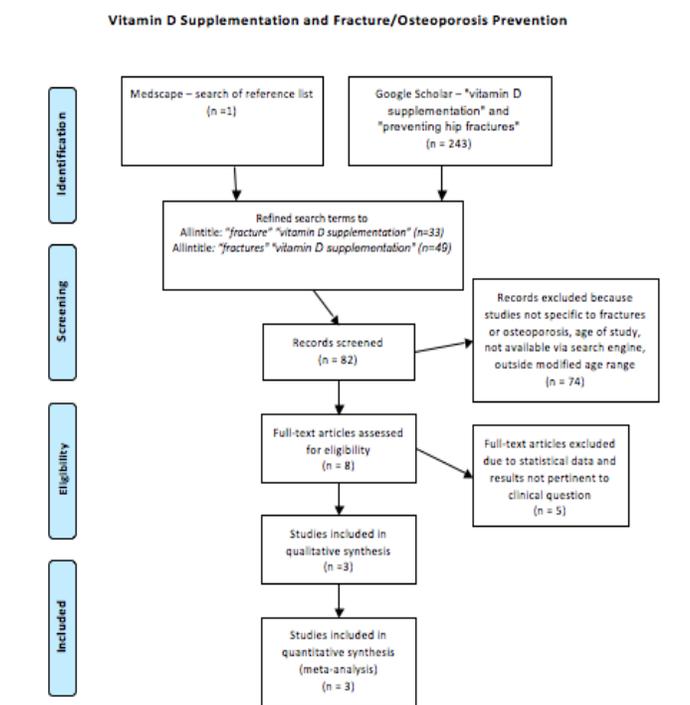
*Comparison – No supplementation*

*Outcome -- Preventing musculoskeletal fractures*

*Clinical Question: In patients ages 65 years and older with Vitamin D Deficiency, is Vitamin D supplementation compared to no supplementation beneficial for preventing musculoskeletal fractures?*

## Methods:

We started our database search using PubMed through the James Madison University library database. Our search terms included “vitamin D” and “screening.” We refined our search to include ages 19 years and older, English language, and published within the past 5 years yielding about 1800 articles. We narrowed our search to include clinical trials, controlled clinical trials, meta-analysis, clinical guidelines, and randomized control



trials. We originally used 50 years old as our cut off age for inclusion. Due to a large search result, we changed the age range to include only patients above age 65 years old in hopes to narrow our search but still resulted in 963 articles. To further narrow our search, we changed our search terms to (vitamin D AND screening) AND osteoporosis to result in 232 articles. Upon initial screening, these articles were not directly related to our clinical question, were performed in foreign countries, or were not accessible through the university database.

We were more successful in our search using Google Scholar. We used search criteria “vitamin D supplementation” and “preventing hip fractures” yielding 243 results. We refined the search to include studies published from 2006-2015. An advanced search using “allintitle”: “fracture” “vitamin D supplementation” resulted in 33 results and another search using “allintitle”: “fractures” “vitamin D supplementation” with 49 results. We chose one article from each of the searches. Our third article to be reviewed was identified by searching the reference list of a Medscape article pertaining to vitamin D.

## **Results:**

**Study 1: Fracture Prevention with Vitamin D Supplementation – A Meta-analysis of Randomized Controlled Trials.**<sup>2</sup> Bischoff-Ferrari H, Willett W, Wong J, et al., Journal of the American Medical Association, May 11, 2005, Vol. 293, No. 18, pgs. 2257-2264

## **Objective:**

The objective of this study was to estimate effectiveness of Vitamin D supplementation to prevent fractures in adults over the age of 60 years old.

## **Design:**

This is a meta-analysis of seven randomized controlled trials identified through searching MEDLINE, Cochrane Controlled Trials Register and EMBASE databases, between 1960 and 2005. Additional studies were also identified through expert consultation, searching reference lists, and the use of medical subject headings. Eligible studies included only double blind randomized controlled trials with a minimum

of one year follow up period (with range of 12 to 60 months) and a mean age of 60 year old patients. The use of oral Vitamin D supplementation, a minimum of one fracture, disclosure of how the fractures were determined, and measurement of 25-hydroxyvitamin D levels during follow up were also requirements to be included in the analysis. The combined studies recruited community dwelling patients, elderly patients living independently in apartments or housing, and nursing home patients resulting in a mean age of 60 years. Studies were excluded if they were uncontrolled trials, observational or animal studies, any condition that would cause for increased falls (stroke, Parkinson disease, steroid therapy, etc), or use of any vitamin D metabolites.

A treatment group receiving vitamin D supplementation with or without calcium supplementation was compared to a placebo group to determine the relative risk of hip fracture or nonvertebral fracture. Of the seven Randomized Control Trials (RCTs) analyzed, two trials administered a 400 IU/day dose to the treatment group while the other five trials administered 700 to 800 IU/day dose. Four of the trials used between 500 and 1200 mg/day supplement of calcium along with the Vitamin D supplement while the remaining three trials recommended intake of three dairy products a day to achieve 800 mg/day calcium intake. Only one control group was provided with a calcium supplement. The outcomes were analyzed using the intention to treat analysis.

### **Results:**

The results of the RCTs in this meta-analysis were separated to include a hip fracture category and a nonvertebral fracture category to be analyzed separately. The relative risk for preventing hip fractures compared to any nonvertebral fracture at any vitamin D dose were 0.88 and 0.83, respectively. There was a significant degree of heterogeneity

Table 1. Hip Fracture Results			
Hip Fracture	RR	Q Test (P value)	NNT
Pooled Data	0.88	0.09 Heterogeneity	
Stratified Data			
High Dose (700-800 IU/d)x	0.74	0.74 Homogeneity	45
Low Dose (400 IU/d)	1.15	0.68 Homogeneity	
RR = relative risk NNT = number needed to treat			

observed in the hip fracture group and the nonvertebral fracture group as evidence by the Cochran Q test ( $P=0.09$  and  $P=0.07$  respectively) and the L'abbe plot (Figure 3 of original meta-analysis).<sup>2</sup> Heterogeneity was defined using the cut off value  $P<0.10$ .

The hip fracture and nonvertebral fracture results were then stratified into separate dose categories to include a low dose (400 IU/day) and high dose (700-800 IU/day) group. Upon stratifying the data, homogeneity was observed (evidence in forest plot in Figure 2 of original meta-analysis) assuming there is similar variance across the studies.<sup>2</sup> The results for each group are summarized in Table 1 and Table 2. For those treated with high doses vitamin D, the number needed to treat based on the pooled risk difference is 45 for experiencing a hip fracture and 27 for experiencing a nonvertebral fracture. This indicated that 45 participants need to be treated with 700-800 IU/d of vitamin D for 24-60 months to prevent one person from obtaining a hip fracture and 27 participants treated to prevent a nonvertebral fracture for 12-60 months.

A sensitivity analysis was performed in addition to the primary analysis to include studies that were excluded from the primary analysis. The sensitivity analysis included two trials that resulted in only one hip fracture and three trials that were less precise in meeting the inclusion criteria. These results are summarized in Table 3. Additional analysis of calcium intake and length of follow up were attempted, resulting in inconclusive evidence. Calcium intake was not provided in the low dose vitamin D trials

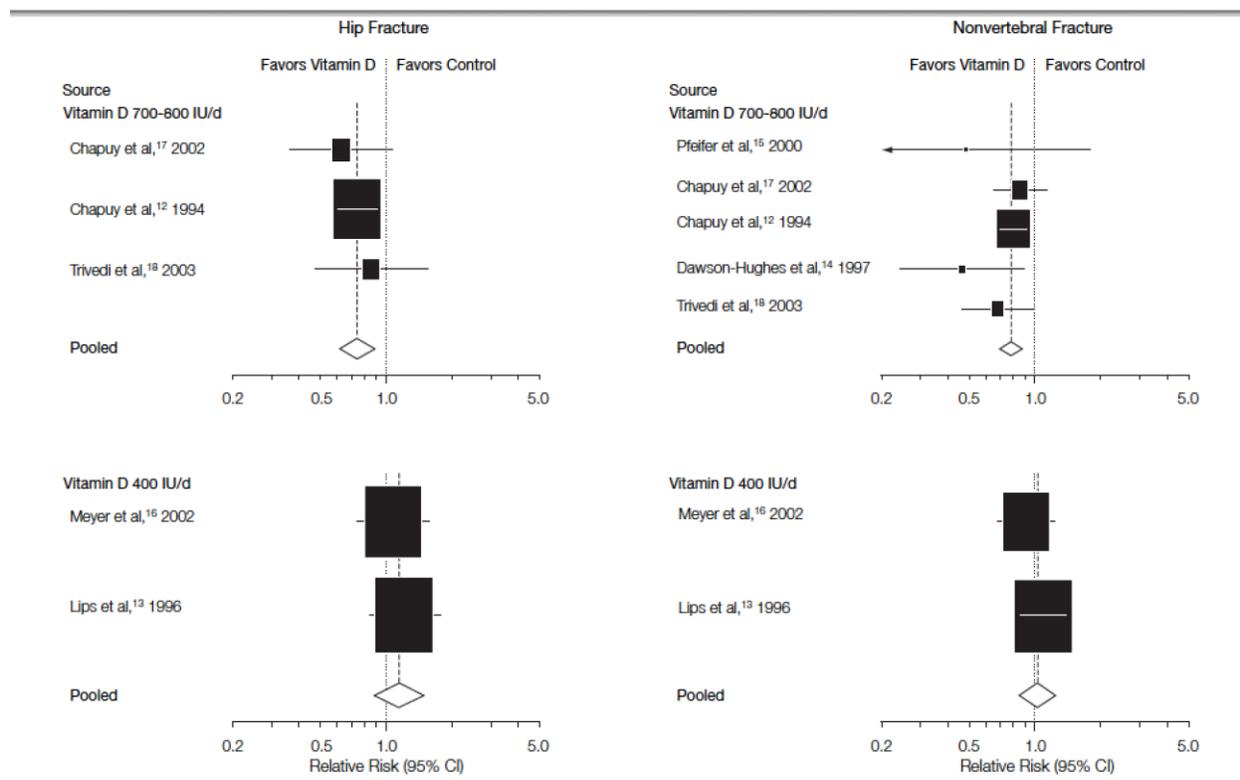
Table 2. Non-vertebral fracture results.

Non-Vertebral Fracture	RR	Q Test (P value)	NNT
Pooled Data	0.83	0.07 Heterogeneity	
Stratified Data			
High Dose (700-800 IU/d)	0.77	0.41	27
Low Dose (400 IU/d)	1.03	0.36	
RR = relative risk NNT = number needed to treat			

Table 3. Sensitivity Analysis for Hip and Non Vertebral Fractures

Relative risk for Hip Fracture	
Pooled data	RR = 0.87
High dose	RR = 0.73
Low dose	RR = 1.15
Relative Risk for Non Vertebral Fractures	
Pooled data	0.83 (P value = 0.13)
High dose	0.77 (P value = 0.40)
Low dose	0.93 (P value = 0.12)

while all but one trial of the high dose trials were given between 500 to 1200 mg of calcium to be taken daily.



Squares represent relative risks (RRs) and size of squares is proportional to the size of the trials. Error bars represent 95% confidence intervals (CIs). Trials are sorted by trial duration ranging from 24 to 60 months for hip fracture and 12 to 60 months for nonvertebral fracture. For 3 trials with hip fractures,<sup>12,17,18</sup> which included 5572 individuals with a vitamin D dose of 700 to 800 IU/d, the pooled RR was 0.74 (95% CI, 0.61-0.88; Q test  $P = .74$ ). For 5 trials with nonvertebral fractures,<sup>12,14,15,17,18</sup> which included 6098 individuals with a vitamin D dose of 700 to 800 IU/d, the pooled RR was 0.77 (95% CI, 0.68-0.87; Q test  $P = .41$ ). For the 2 trials,<sup>13,16</sup> with a vitamin D dose of 400 IU/d, trial duration ranged from 24 months to 36 to 41 months.

- Bischoff-Ferrari, Willett, Wong, Giovannucci, Dietrich, Dawson-Hughes. Fracture prevention with vitamin D supplementation. *JAMA*. 2005;293(18).

Overall, results of this meta-analysis suggest Vitamin D administered at higher doses reduce hip fractures by 26% and nonvertebral fractures by 23%, based on the calculated relative risks. Lower dose Vitamin D does not show to have favorable outcomes in reducing fractures.

### **Critique:**

This meta-analysis includes seven RCTs, each with large sample sizes to include 9,280 participants in total. Larger sample sizes are more effective in representation of the population. Other strengths of this study include the age range which is pertinent to

our target population in our research question, inclusion of males and females, and double blinding randomization.

The sensitivity analysis that was performed to include 3 additional studies regarding non-vertebral fractures nearly doubled the number of participants. The relative risks for any non-vertebral fracture remained the same for the pooled data and high dose group while the relative risk in the low dose group decreased to 0.93. These results are consistent with the primary analysis and increase the sample size to increase statistical power.

Negative attributes include the use of non-English, non-US studies and the age of the meta-analysis. The use of non-English, non-US studies impedes data extrapolation because they may not pertain to our patient population as there may be different risk factors for osteoporosis and vitamin D deficiency in other parts of the world. This article was published in 2005 and analyzes studies that were performed between 1993 to 2004, which are over a decade old. Current research has conflicting views with the recommendations of daily levels of vitamin D that should be consumed. This research used daily doses of 400 IU/day of vitamin D, which was the recommendation for adequate bone health at that time. The 2010 recommendations for daily vitamin D ingestion, per the Institute of Medicine (IOM) and the National Osteoporosis Foundation (NOF), consist of higher values. The IOM recommends 600 IU/day for individuals 18-70 years old and 800 IU/day for individuals 70 years or more. The NOF recommendations are even higher with 800-1,000 IU/day for individuals 50 years or older.

Cochran Q test is a statistic based on the Chi squared test. Limitations to this statistic are its poor power for determining true heterogeneity, hence the P value for significance is 0.10 (rather than 0.05).<sup>3</sup> Additional limitations to the Q test are that it does not give information regarding the strength between the variables, and it is sensitive to the sample size of the studies.<sup>4</sup> Q tests have low power when there are too few studies and high power with too many. Rather than using the Cochran Q test, the more recently developed I<sup>2</sup> value is more reliable and more commonly preferred.

Lastly, not all of the studies stratified their data according to sex, and all trials were performed on predominantly white populations so data is limited, pertaining to the

benefit in different genders and races. The independent effect of vitamin D could not be determined due to the additional calcium administration being inconsistent among the studies. Follow up period for inclusion in this meta-analysis required one year with an average of about 2 years. There could be some question whether that is an adequate duration for positive results.

**Study 2: Calcium plus Vitamin D Supplementation and the Risk of Fractures.**<sup>5</sup>

Jackson R, La Croix A, Gass M, et al., New England Journal of Medicine, February 16, 2006, Vol. 354, No. 7, pgs. 669-683

**Objective:**

The objective of this paper was to assess the primary hypothesis that postmenopausal women randomly assigned to a calcium plus vitamin D supplementation group versus a control group would reduce the risk of fractures, specifically hip fractures with further consideration of clinical vertebral fractures or lower arm/wrist fractures.

**Design:**

This study consisted of 36,282 postmenopausal women, ages 50 to 79 years of age, that were randomly assigned by double blind fashion to active supplementation of 1,000 mg calcium and 400 IU vitamin D<sub>3</sub> per day (n=18,176) versus a placebo group (n=18,106). The trial began with subject allocation between 1995 - 2000 and concluded in 2005. Follow up took place over a nine year period (mean response of seven years). These women were recruited from Women's Health Initiative (WHI) Dietary Modification trials, WHI Hormone Therapy trials or both. Exclusion criteria for trial prospects included hypercalcemia, renal calculi, corticosteroid use, and calcitriol use. The trial did allow for supplemental use of up to 1,000 mg Ca<sup>2+</sup> per day and up to 600 IU vitamin D per day, as well as bisphosphonates and calcitonin.

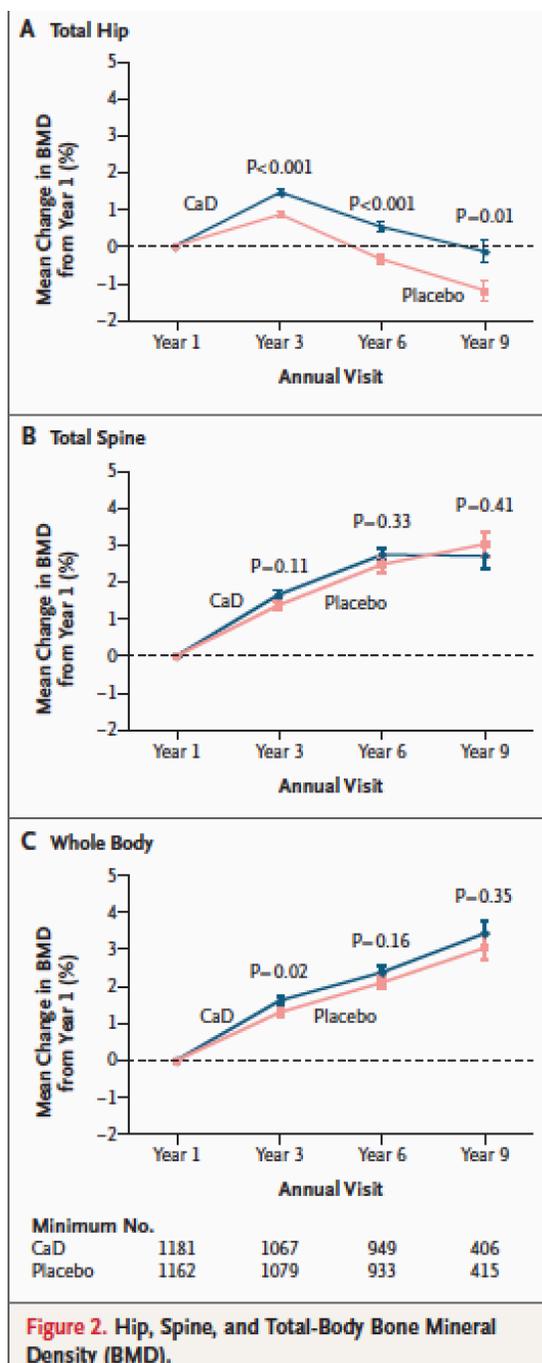
Baseline assessment, prior to randomization, consisted of a questionnaire concerning calcium and vitamin D intake of dietary, supplemental and prescription medication use. Blood samples of 25-hydroxyvitamin D levels were also acquired at

this time. Bone mineral density was tested in a sub-group at randomization and at annual visits 3, 6, and 9.

Participants were instructed to take chewable or swallowable tablets containing 500 mg of calcium carbonate and 200 IU of vitamin D<sub>3</sub> bi-daily with meals to maximize absorption. Performance analysis was investigated at six month phone calls or clinic visits and at annual visits. Patient medication compliance was assessed by weighing pill bottles at clinic visits. 25-hydroxyvitamin D levels were measured with DiaSorin Liaison chemiluminescent immunoassay system. Clinical fractures were recorded as any fracture other than ribs, sternum, skull or face, fingers, toes, or cervical vertebrae and were verified by review of radiology, MRI or operative reports by blinded, trained physicians.

### Results:

The study ended in 2005 with 4.3% of the study population being deceased and 2.7% lost to follow up. Within the first three years of follow up, adherence to the study medication regimen, classified as continued use of 80% or more of the study medication, was 60-63% and an additional 13-21% were compliant with 50% of the medication regimen. When the study ended, 76% were still taking some amount of the study medication with 59% still adherent to the originally prescribed levels of 80% or more.



- Jackson, LaCroix, Gass, et al. Calcium plus vitamin D supplementation and the risk of fractures. *New England Journal of Medicine*. 2006;354(7):669-683.

Bone mineral density (figure 2) of the total hip (A), total spine (B) and whole body (C) were analyzed at annual visits 3, 6 and 9. Bone mineral density of the hip proved to be the best outcome of the entire study with values in favor of treatment with calcium and vitamin D. Average differences between treatment groups were 0.59% and 0.86% at years 3 and 6 respectively (p-value - <0.001) and 1.06% at year 9 (p-value - <0.01). Bone mineral density of the total spine and whole body were insignificant between study groups.

Fracture analysis over the mean seven year follow up (intention-to-treat analysis) saw a total fracture count of 2,102 for the calcium and vitamin D study group versus 2,158 within the placebo group (HR - 0.96). Hazard ratios (HR) are a measure of the strength of a relationship produced by proportional hazard regression and may be interpreted as a relative risk adjusted for multiple confounding variables. Hip fractures of the study group consisted of 175, whereas the placebo group had 199 making this the lowest hazard ratio of 0.88. Clinical vertebral fractures were 181 for the study group and 197 for the placebo (HR - 0.90) and lower arm/wrist fractures were 565 for the study group and 557 for the placebo (HR - 1.01). An additional comparison was made between the treatment group and placebo group at six months after they were observed to be noncompliant with the medication regimen. Hip fractures were found to have an even lower hazard ratio of 0.71, with 68 fractures in the study group and 99 fractures in the placebo group. No significant difference was found between the vertebral, lower arm/wrist or total fracture groups.

Overall analysis found a higher likelihood of hip fracture for women in the age group of 50-59 yo with a hazard ratio of 2.17 (95% CI - 1.13-4.18). Statistical significance was also present with study group participants who had sustained zero falls within the past 12 months with a hazard ratio of 0.74 (95% CI - 0.56-0.98) versus one fall with a hazard ratio of 0.96 (95% CI - 0.62-1.49). The study medication regimen was correlated with an adverse outcome of renal calculi found in 449 women in the study group versus 381 women in the placebo group with a hazard ratio of 1.17 (95% CI - 1.02-1.34).

**Critique:**

Positive attributes that pertain to this article consist of a large study population (n=36,282) which at the time, was the largest its size for this particular research. Bias and influence was minimized and/or negated through the use of randomization of study population allocation to specified research groups. There was an average of seven years of follow-up for study participant analysis of research outcomes, which allowed for a thorough understanding of the effectiveness of the implemented calcium and vitamin D therapy. In relation to the assessment of bone mineral density, cross calibration of the dual-energy x-ray absorptiometry machinery was measured to ensure comparability of studies from the different testing centers.

Negative attributes in relation to this research starts with the release of this article being almost a decade old. As addressed above, this is a cause for concern because recommendations for daily vitamin D intake have changed over the past several years. The diversity of this study was lacking with the study participants being 83% Caucasian. Participants were allowed to use supplemental calcium and vitamin D outside the amounts being administered, but there was no discussion of how they were accounted for. Participants were also permitted to take other hormone medications such as estrogen, bisphosphonates and calcitonin, as they were recruited from a Women's Health Initiative study. The additional supplements that may or may not have been adequately accounted for and the hormone medications that could modify calcium and vitamin D levels both have the potential to create variables that could alter the results of this study.

**Study 3: Treatment of Vitamin D Insufficiency in Postmenopausal Women - A Randomized Clinical Trial.**<sup>6</sup> Hansen K, Johnson E, Chambers K, et al., Journal of the American Medical Association, August 3, 2015, Vol. 175, No. 10, pgs. 1612-1621

**Objective:**

The objective of this research article was to investigate the effects of high and low dose cholecalciferol on total fractional calcium absorption (TFCA) – the percentage of a given dose of calcium that is absorbed by the GI tract, bone mineral density (BMD),

and muscle fitness after one year in postmenopausal women with vitamin D insufficiency.

**Design:**

This study is a randomized control trial including 230 postmenopausal women ages 75 and younger. These women were recruited via local advertisements, and eligibility was determined based on telephone screening and screening serum measurements of serum 25(OH)D, calcium, albumin, creatinine and parathyroid hormone levels. Inclusion and exclusion criteria are summarized in Table 4. Eligible participants were

Table 4. Study Inclusion and Exclusion Criteria.
Inclusion Criteria
<ul style="list-style-type: none"> <li>• 25(OH)D level of 14ng/mL – 27n/mL</li> <li>• &gt;5 years post menopausal or oophorectomy</li> <li>• 60 years or older if pervious hysterectomy w/o oophorectomy</li> </ul>
Exclusion Criteria
<ul style="list-style-type: none"> <li>• &gt;75 years old (associated with intestinal resistance to vit d)</li> <li>• Hypercalcemia</li> <li>• Nephrolithiasis</li> <li>• Cancer w/in 5 years (excluding skin)</li> <li>• Inflammatory bowel disease</li> <li>• Malabsorption</li> <li>• Celiac sprue</li> <li>• Chronic diarrhea</li> <li>• Glomerular Filtration Rate &lt; 45mL/min</li> <li>• Adult fragility</li> <li>• Fracture of hip, spine or wrist</li> <li>• Use of bisphosphonates, estrogens, calcitonin, teriparatide, oral corticosteroids, anticonvulsants, or cholcalciferol &gt;400IU/d</li> <li>• Diabetes mellitus</li> <li>• Bone mineral density T score -2.5 or less</li> </ul>

educated to consume 600 to 1400 mg/d of calcium via diet or supplementation and were advised to complete a 4 to 7 day diet diary within the first month of the study.

Participants were stratified by high Parathyroid hormone (PTH) level and calcium intake greater than 1000 mg/d then were randomized into a high dose, low dose, or placebo group. The high dose treatment group received a loading dose of 50,000IU/d for the first 15 days to raise their 25(OH)D levels to above 30 ng/mL. The low dose and placebo groups were also given a placebo loading dose for the first 15 days to maintain masking. Following the loading dose administration: the high dose group was given a

yellow high dose capsule to be given every 15th day with a white placebo capsule to be taken daily, the low dose group was given a white low dose capsule to be taken daily and a yellow placebo to be taken on every 15th day, and the placebo group was given white capsules for daily consumption and yellow placebos for every 15th day. Adherence was measured by counting the pre-filled pill boxes.

The primary outcome measured in this study was change in TFCA after one year using the gold standard dual stable calcium isotope method (tracking of renal reabsorption and endogenous fecal calcium excretion). BMD was the secondary outcome measured, using the Lunar bone densitometry machine.

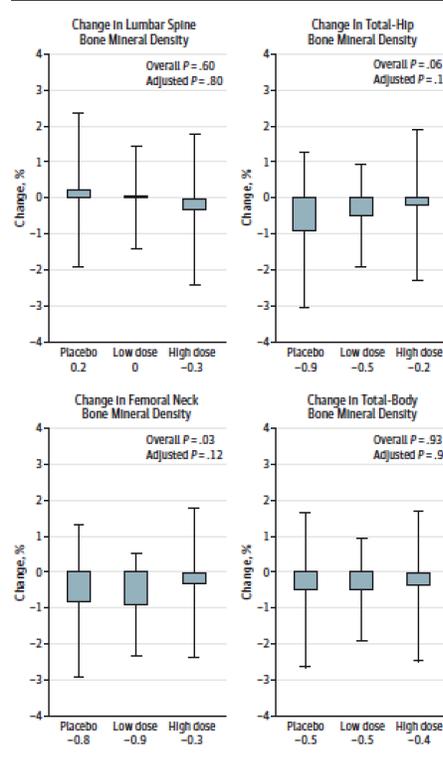
Participants followed up at 30, 60, 120, 240, and 365 days for 25(OH)D, calcium, 24-hour urine calcium levels, Timed Up and Go (TUG) (mobility assessment), and five sit-to-stand (STS) tests (lower limb strength assessment). Also recorded at each visit were pain rated on 10 point pain scale, functional status, activity level, and adverse events (ex: nephrolithiasis, fracture, infection, or hospitalization). During analysis of the high dose treatment group, if any of the participants' 25(OH)D level dropped below 30 ng/mL then their cholecalciferol dose was adjusted to reach the therapeutic range of greater than 30 ng/mL (placebos were given to a group of the participants to maintain masking).

### Results:

Upon resolution of this one year study, nine women (3.9%) had withdrawn due to personal reasons, leaving the final study count at 221 participants. Mean 25 (OH)D serum levels showed considerable variance between comparison groups at follow up visits. The placebo group had a serum level of 19 ng/mL, low dose

R. Chambers K, et al. Treatment of vitamin D insufficiency in postmenopausal women: A randomized clinical trial.

Figure 3. Annualized Percent Change in Bone Mineral Density by Treatment Assignment



- E. Hansen K, Erin Johnson R,

cholecalciferol group had 28 ng/mL and the high dose cholecalciferol group had 56 ng/mL (p-value - < 0.001). The study participants had a near perfect compliance rate with the medication regimen throughout the duration of the study.

TFCA was shown to increase in the high-dose study group (0.6%) and decreased in the low-dose study group (4.5%) and placebo group (0.9%). Baseline calcium absorption models were used to adjust for variance in baseline TFCA between study groups. These models showed a 1% increase in the high-dose group and decreases of 2% in the low-dose group and 1.3% in the placebo group.

No significance was found in comparison of groups in relation to bone mineral density (Figure 3) for lumbar spine, hip or total body bone mass density, although a minor change was noted in femoral neck bone mineral density.

### ***Critique:***

Strengths that can be credited to this study consist of it being a randomized, double-blind, placebo-controlled trial which allowed for elimination of bias. This study was published in 2015, so it is the most recent research conducted and is the most up to date on recommended practices. Loss of participants was minimal with a 4% attrition rate (9 individuals), while adherence rate to the research medication requirements was 100% with the remaining 221 individuals staying compliant throughout the entire study. One of the major inclusion criteria was establishing baseline vitamin D deficient participants (14-27 ng/mL) prior to starting the study to allow for a balanced comparison between individuals. The study allowed personal calcium management of 600-1,400 mg/day which falls in line with current recommendation from IOM of 1,200 mg/day. This research compared “low-dose” cholecalciferol of 800 IU/day (22,400 IU/mo) vs “high-dose” 50,000 IU/ bi-monthly (100,000 IU/mo) vs placebo. Current recommendations from the Institute of Medicine are 600-800 IU/day and the National Osteoporosis Foundation are 800-1,000 IU/day. High level vitamin D therapy administration allowed for a better understanding of potential outcomes according to current recommendations. The exclusion criteria for this study was very thorough by prohibiting patients that had diabetes mellitus; osteoporosis; hypercalcemia; nephrolithiasis; cancer within 5 years (excluding skin CA); inflammatory bowel disease; malabsorption; celiac sprue; chronic

diarrhea; glomerular filtration rate <45 mL/min; adult fragility; fracture of the hip, spine or wrist; use of medications that modify bone integrity within the past 6 months (bisphosphonates, estrogens, calcitonin, teriparatide, oral corticosteroids, anticonvulsants or cholecalciferol doses greater than 400 IU/day); and bone mineral density T-scores -2.5 or less.

This study presented with a few weaknesses worth mentioning. The study size was considerably small (n=230) and took place in a single center in south-central Wisconsin, which limits its ability to extrapolate data for greater populations. Its duration took place over one year which doesn't allow for greater insight into long term effects of vitamin D therapy administration. The study population was poorly diversified with 90% Caucasian, 6% African American, 2% Asian, 1% Indian/Alaskan, and 1% Hispanic and is, therefore, limited in its applicability to more realistic populations. The research focused primarily on bone mineral density and calcium absorption and had no discussion of vitamin D deficiency's effects on the presence of fractures, which is of particular interest to our research. The study population was only women with a maximum age of 75 years old which is limited in its applicability to our study population.

### **Discussion:**

Vitamin D is important for bone health as it promotes calcium absorption, maintains serum calcium and phosphate levels and allows for normal bone mineralization.<sup>7</sup> Little evidence is available as to when the appropriate time to begin screening for vitamin D deficiency and if the long term effects of supplementation are beneficial. Although calcium is the most common contributor to osteoporosis, vitamin D deficiency contributes equally by insufficient calcium absorption.<sup>7</sup> The purpose of this review is to determine if supplementation of vitamin D is beneficial in preventing bone fractures.

The results of the three studies varied, but each had a specific positive outcome. All studies showed that the higher level vitamin D and calcium groups had better end results than that of their comparisons. Bischoff et al showed that, after stratification, the high dose vitamin D (700-80 IU/day) group had the lowest relative risk value with 0.74 for hip fractures versus its comparison group (400 IU/day) with a relative risk value of

1.15. Jackson et al found that its supplementation group (vitamin D - 400 IU/day; calcium - 1,000 mg/day) had better long-term total hip bone mineral density than placebo group over the mean seven year follow-up period with mean differences between study groups of 0.59% at year 3, 0.86% at year 6 and 1.06% at year 9. Statistical significance was found at years 3 and 6 with a p-value of 0.001 and year 9 with a p-value of 0.01. Hansen et al demonstrated that, after controlling for baseline calcium absorption levels, its high dose vitamin D group (100,000 IU/mo) had increases of total fractional calcium absorption (TFCA) of 1% while the low dose group (800 IU/day) and placebo had decreases in TFCA of 2% and 1.3% respectively.

Jackson et al had the longest follow up period at seven years compared to Bischoff et al with an average of 2 years and Hansen et al with one year follow up. A seven year follow up period permits for thorough understanding of the effectiveness of the implemented therapy. Jackson et al had its lowest hazard ratios among hip fractures between the supplementation group and placebo of 0.71 (95% CI – 0.52-0.97) when analyzing participants six months after being noncompliant with the medication regimen. This hazard ratio increased to 0.88 (95% CI – 0.72-1.08) among the same group when analyzed over the mean seven year follow up period. With shorter follow up periods, there is inconclusive evidence regarding adequate time for a maximum response to therapy.

Compliance in Jackson et al and Hansen et al were reported, but no data was published regarding compliance for the individual meta-analysis studies. Hansen et al had a considerably smaller sample size but nearly 100% compliance. Jackson et al was significant for increased risk of renal calculi but also administered calcium 1,000 mg/day and allowed an additional calcium 1,000 mg/day at the discretion of the participant, making it potentially the largest calcium administration of the three studies.

Jackson et al and a few of the RCTs included in the Bischoff et al meta-analysis were provided with calcium supplementation which was regulated through the trial. However, Jackson et al also allowed for the consumption of additional calcium, bisphosphonates, and estrogen which were not accounted for throughout the study. Hansen et al had strict exclusion criteria restricting the use of bisphosphonates, estrogen, vitamin d >400 IU/d, calcitonin, etc. Although Hansen et al did not provide

calcium supplementation to their treatment groups, they were recommended to consume between 600-1400 mg/day.

There is currently no established definition of vitamin D deficiency with threshold values existing between either <20 ng/mL to <30 ng/mL. Neither Bischoff et al nor Jackson et al began their studies with stated baseline vitamin D levels for inclusion/exclusion criteria, whereas Hansen et al established baseline vitamin D levels for all participants of 14-27 ng/mL to create a uniform population for analysis.

There is currently no industry reference standard for testing for vitamin D. As stated in the USPSTF, multiple assays exist such as competitive protein binding, immunoassay, high performance liquid chromatography or combined high performance liquid chromatography and mass spectrometry. Throughout our research, testing for vitamin D was not similar between any of our studies. The first study did not define which assays were used across any of the studies reviewed in the meta-analysis. The second study stated that vitamin D was tested using the Dia Sorin Liaison chemiluminescent immunoassay, while the third study used high performance liquid chromatography. The third study claimed that its high performance liquid chromatography assay is one of two gold standard assays, but the USPSTF statement contradicts this claim. Without an established industry “gold standard” for cross study comparison, there is no definitive way to make assertions that participant vitamin D values are comparable.

Recommended daily vitamin D supplementation is also a debatable point. The Institute of Medicine endorses daily vitamin D levels of 600 IU/day for ages 18-70 and 800 IU/day for older than 70 years. The National Osteoporosis Foundation suggests 800-1,000 IU/day for persons over the age of 50. These recommendations were released in 2010. The first two studies were published in 2005 (Bischoff et al) and 2006 (Jackson et al), and the chosen vitamin D levels allotted to study participants were commensurate with the recommended practice of the time. Bischoff et al consisted of seven studies in total within the meta-analysis, with two studies administering 400 IU/day of vitamin D and the five other studies administering 700-800 IU/day, while Jackson et al issued 400 IU/day of vitamin D to its participants. Hansen et al, however, had a low dose (800 IU/day vitamin D) cohort and a high dose (100,000/month vitamin

D) cohort. Comparing current recommendations to previously suggested therapeutic levels would lend itself to increased vitamin D quantities being better for ideal bone health. Unfortunately, none of these studies found convincing, statistically relevant data that would support this assumption.

<b>Table 5. Overall Comparison</b>			
	Bischoff et al	Jackson et al	Hansen et al
<b>Study population</b>	9,280	36, 282	230
<b>Age of participants</b>	≥ 60 years old	50-79 years old	≤ 75 years old
<b>Calcium Administered</b>	4 @ 500-1,200 mg/day 3 @ 800 mg/day	1,000 mg/day	600-1400 mg/day
<b>Vitamin D administered</b>	2 @ 400 IU/day 5 @ 700-800IU/day	400 IU/day	Low dose – 800IU/day High dose – 50,000 bimonthly
<b>Duration of Study</b>	Meta-analysis 1960-2005	1995-2005	2010-2014
<b>Length of Follow up</b>	Minimum one year Average ~2 years	7 years	1 year
<b>Compliance</b>	N/A	~76%	Nearly 100%

### **Conclusion:**

The summation of our investigation into vitamin D deficiency and presence of musculoskeletal fractures has proven to be relatively inconclusive. The resulting data from our three studies did not provide any definitive proof that improved vitamin D levels

correlates with better bone health. Bischoff et al concluded that the use of vitamin D 700-800 IU/day would reduce the risk of hip or any non-vertebral fracture by approximately 25% but did not correlate the benefit of calcium administration. Jackson et al stated that following its research, calcium with vitamin D administration did improve hip bone mineral density, but there was no statistically significant reduction in hip fractures, nor clinical vertebral fractures, fractures of the lower arm or wrist, or total fractures. Hansen et al made a final decision that due to their research, there was a minor improvement of calcium absorption in the high dose vitamin D arm of their study but realistically provided no meaningful benefits to overall bone mineral density. Furthermore, they stated that a significant increase in calcium absorption is needed to improve bone mineral density and reduce fracture risk.

The importance of screening tests is for the prevention of adverse health outcomes. In relation to health screenings of vitamin D levels, the current lack of industry standard for official classification of “deficiency” (<20 ng/mL vs < 30 ng/mL) creates a subjective environment of one patient requiring supplementation, while another would not. Furthermore, a “gold standard” assay has not been established to allow for continuity between individual patient evaluations by separate practitioners. Our research showed that there was no statistical significance between higher vitamin D administration and fracture prevention but there was a positive correlation. A vitamin D screening test might be in order for patients at a particular age, say 65 years old when Medicare benefits can commence. This could provide baseline values on a practitioner-by-practitioner basis for future assessment as osteoporosis and fall fractures become more prevalent in older populations.

Our recommendation to BR about her inquiry into vitamin D supplementation for reduction of hip fracture risk when she has a vitamin D level on the low end of normal (if deficiency is classified as <20 ng/mL), is clinically asymptomatic, and has positive family history for osteoporosis would be the positive “potential” benefits of supplementation. This conversation could be framed with the understanding that there are no guarantees about risk reduction, a positive correlation/association exists, and the only negative outcome potential would be renal calculi.

There is an upcoming clinical trial scheduled to begin in January of 2016, titled “Effects of Vit D Fortification on Vit D Metabolite Profiles and Status in Vit D Insufficient Individuals” (ID# - NCT02422784). Hopefully, this trial will provide more conclusive evidence regarding the benefit of vitamin D to better provide clinically applicable recommendations.

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