Title: Assessing the Validity of Vitamin D Supplementation in Patients with Symptomatic Knee Osteoarthritis

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1. Reference:

2. Clinical Question: In an older adult population, does supplementation of 25-hydroxyvitamin D for patients with symptomatic knee osteoarthritis with low serum vitamin D alleviate symptoms of the disease?

PICO Parts:
P – Adults aged 50-80 with symptomatic knee osteoarthritis and low serum vitamin D levels
I – 25-hydroxyvitamin D supplementation
C – Placebo
O – Decrease in pain, cartilaginous changes, and further joint degeneration in the affected knee

3. Search Strategy

a. Database(s) searched: Pubmed

b. Keyword Search Terms used: osteoarthritis, vitamin D, supplementation, randomized controlled trial

c. MeSH Search Terms used: N/A

d. Limits used: 5 years, humans, English

e. Complete search strategy: (((“osteoaarthritis”[MeSH Terms] OR (((“osteoaarthritis”[MeSH Terms] OR ”osteoaarthritis”[All Fields]) AND (“vitamin
4. Methods Description (setting, population, sample size, study design):
The study design was a randomized, double blind, placebo-controlled trial. It was conducted between June 2010 and December 2013 in Tasmania and Victoria, Australia. Participants (N=413) were recruited from June 2010 to December 2011 via advertisements in local media and referrals from numerous GPs, rheumatologists, and orthopedic surgeons. Inclusion criteria included: 1) participants aged 50-79 years, 2) symptomatic knee osteoarthritis for at least six months according to American College of Rheumatology Criteria, 3) ACR function of I-III (all able to perform self-care activities), 4) good health correlating to either 1 or 2 as scored by a Likert scale 1-5, and 5) serum 25-hydroxyvitamin D levels between 12.5-60 nmol/L. Exclusion criteria included: 1) co-occurring morbidities including cancer, psoriatic/rheumatoid arthritis, cardiac/renal/gastrointestinal impairments, 2) grade 3 radiographic impairments, 3) severe pain on standing, 4) anticipated knee or hip surgery within 2 years, 5) hypersensitivity to vitamin D, 6) history of severe knee trauma, 7) conditions affecting oral drug absorption, and 8) history of vitamin D supplementation or investigational drugs within 30 days prior. With the stringent inclusion/exclusion criteria, 599 participants received phone screenings, and of those 599, 186 were excluded based on meeting one or more exclusion criteria. Fifty percent of the included participants were women. Of the 413 included, 209 were randomized to receive vitamin D, and 204 were randomized to receive placebo.

5. Methods Interpretation (Validity):
   a. Was there an independent “blind” comparison with a reference standard? - Yes, the trial was a double blind study utilizing an identical placebo to the Vitamin D supplementation. The patients were placed into groups utilizing a 1:1 ratio that was computer generated, and they were concealed from the investigators, researchers, and participants until the end of the study.

   b. Did the sample include an appropriate spectrum of patients to whom the treatment will be applied in clinical practice? - The sample was appropriately large with 413 patients, with 209 of them receiving the Vitamin D intervention. Sample size calculation assumed α=0.05 and β=0.20 and was based on the Cohen’s formula for effect size. With an N=400, a 20% dropout would have allowed for a power of 80% to detect differences in medial tibial cartilage loss and self-reported pain on the WOMAC scale. Fifty percent of the sample were women in each group, giving an appropriate gender comparison for both the placebo and the vitamin D intervention. Finally, the patient population was pooled from multiple different medical centers and community groups across two discrete areas of the
country. Overall, this study includes a generalizable cross section of the population of southern Australia.

c. Did the results of the treatment being evaluated influence the decision to treat with the reference standard? - In this study, the investigators were blind to treatment of the patients until the results of the study were released. The medications were concealed by a central automated allocation procedure, which also aided in the blinding of the investigators. Because of this, procedure bias was avoided.

d. Were the methods for performing the treatment described in sufficient detail to permit replication? - Yes. The research staff was provided with a standard protocol and case report form and was trained to competently administer items as per protocol. Detailed assessment protocols for the following measurements were included: cartilage volume change, cartilage defects, bone marrow lesions, knee pain/WOMAC scoring, meniscal tear, meniscal extrusion, lower limb strength, core muscular strength, upper arm BP, central BP, aortic stiffness, physical activity, body fat, hand grip strength, radiographic osteoarthritis, and serum 25-(OH) D levels. The source listed below is the published protocol used for this RCT.


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6. Results:
25-hydroxyvitamin D levels increased significantly more in the vitamin D treatment group (40.6 nmol/L) than in the placebo group (6.7 nmol/L) (P < 0.001) over the two years of the study. However, there were no significant differences in either the primary outcomes (change in tibial cartilage volume and WOMAC pain score) or the secondary outcomes (change of tibiofemoral cartilage defects or change in tibiofemoral bone marrow lesions). Therefore, the findings from the study do not support the use of vitamin D supplementation for preventing tibial cartilage loss or improving WOMAC knee pain score in patients with symptomatic osteoarthritis of the knee.

7. Translational applications (How does this study apply to your patients? Be specific regarding a T1-T4 level):
This study is a T3 level on the Clinical and Translational Research Spectrum. It represented clinical outcomes research based on a subset of the population that was treated for their vitamin D deficiency. The results of the study were adequate with statistical significance. Due to the call for more regulated RCTs from recent meta-analyses and reviews on current literature, the investigators of this study applied stringent inclusion and exclusion criteria that were strictly enforced. This strengthened the causality of the results of the treatment. In addition, the sample size and population...
was adequate and symmetrical for both the placebo and treatment groups, the study was double blind, and the groups were randomized. This increased generalizability and strength of the results. The methods were clearly reported, so the study could be easily reproduced. Based on the thorough nature of this study, we recommend following the guidelines concluded by this study to avoid vitamin D supplementation in patients with knee osteoarthritis to avoid its adverse side effects. We would, however, like to see this study reproduced in the United States, as geographical location and cultural differences may play a role in the effects of treatment. In addition, it would be beneficial to see if the data could be reproducible using the stringent inclusion/exclusion criteria these investigators proposed, as this is some of the first data from a larger, reliable RCT since recent meta-analyses.