Effect of Vitamin D3 on self-perceived fatigue: A double-blind randomized placebo-controlled trial

BACKGROUND:

- Vitamin D deficiency is frequent and has been associated with fatigue in uncontrolled trials. Fatigue can be associated with impaired quality of life and loss of productive work time. Physicians prescribe medications like vitamin D to try and help with the fatigue even with the small amount of evidence supporting this practice.

OBJECTIVE

- To test if a single vitamin D dose improves fatigue after 30 days among vitamin D deficient individuals who report fatigue but are otherwise healthy.

METHODS

- **Design**: A double-blind randomized placebo-controlled trial. Duration: 4 weeks.
- **Inclusion criteria**: Healthy subjects who suffered from fatigue of 20 to 50 years with a body mass index (BMI) of 18 to 25 kg/m^2
- **Exclusion criteria**: Exclusion criteria were intake of vitamin D preparations during 8 weeks prior to study enrollment, pregnancy or lactation, hypersensitivity to vitamin D, any known cardiovascular, pulmonary, renal, or hepatic disease, anemia, hyper- and hypocalcemia (corrected serum calcium levels >2.54 mmol/L or <2.09 mmol/L, respectively, the normal range given by the local laboratory), presence of muscle or bone disease, severe infection, inflammation, malignancy, known mental disorders, sleep disorders, chronic intake of concurrent medication, except oral contraceptives, known chronic kidney disease with glomerular filtration rate (CKD-EPI-estimated) <60 $mL/min/1.73m^2$, medication affecting physical or mental performance, participation in any other therapeutic trial within the previous month, inability to follow the procedures of the study, for example, due to language problems, psychological disorders, dementia etc., enrollment of the investigator, his/her family members, employees, and other dependent persons
- **Primary outcome measure**: Intra individual change in the fatigue assessment scale (FAS) from baseline to 4 weeks
- **Secondary outcome measures**: The safety of oral administration of vitamin D based on clinical (physical examination, adverse events) and laboratory (serum parathyroid hormone [PTH], calcium, and phosphate levels) findings and the efficacy of vitamin D administration on fatigue using a short self-developed fatigue test
- Each patient had a baseline visit. At this visit, the FAS questionnaire was completed by the participant. Blood pressure was measured after 5 minutes' rest in a sitting position. Blood was taken to determine 25(OH) D (calcifediol), intact PTH, serum phosphate, and serum calcium. Following this, a single oral dose of 100,000 units of vitamin D (2 capsules each containing 50,000 IU) or placebo (two capsules containing placebo) was administered, supervised by the study MD. 58 patients received in the Vitamin D and 62 received the placebo.
- The follow-up visit took place 4 weeks (+ maximum 7 days) after the baseline visit and ingestion of the study medication. Again, the FAS questionnaire was filled in by the participant. Additionally, FCA was applied

- Power 80% with an alpha level of 0.05 to detect a 20% difference in the percentage change between the 2 groups. A minimum of 25 patients per group would need to be enrolled
- Data handling method was per protocol

RESULTS

- One participant was excluded from the analysis according to the protocol due to starting venlafaxine after the baseline visit, 1 participant was lost to follow-up. In total, 120 participants (58 in the vitamin D and 62 in the placebo group) were included into per-protocol analysis
- **Primary outcome measure**: The mean FAS decreased significantly more in the vitamin D group (−3.3±5.3; 95% confidence interval [CI] for change −14.1 to 4.1) compared with placebo (−0.8±5.3; 95% CI for change −9.0 to 8.7); (P=0.01). FAS improved significantly only in the vitamin D (P<0.001) but not in the placebo (P=0.24) group. Amelioration of fatigue was reported more frequently in vitamin D than in placebo group (42 [72%] vs 31 [50%]; P=0.01; odds ratio [OR] 2.63, 95% CI for OR 1.23–5.62)
- **Secondary outcome measures**: Improvement in fatigue at the 4 weeks' follow-up visit, as assessed by the self-developed FCA, was reported by 28 (48%) of vitamin D treated and 23 (37%) of placebo-treated patients (P=0.22) (OR 1.58; 95% CI for OR 0.76–3.28)

  A significant increase in 25-OH vitamin D was observed in vitamin D but not in placebo-treated participants (14.0±5.4 vs −0.3±3.2μg/L; P<0.001). A significant decrease in PTH levels in vitamin D-treated and an increase in placebo-treated participants was observed (−2.6±13 vs 3.9±18ng/L; P=0.03). Calcium and phosphate levels remained unchanged in both groups

  The number of participants reporting adverse events and the number of adverse events per patient was similar in both groups. No serious events occurred. The most often reported adverse event was infection, the majority viral upper respiratory likely due to the influenza outbreaks in spring and winter 2014 and 2015, when the most patients were recruited.
- **Author's conclusion:** A single dose of oral 100,000 IE vitamin D3 is an effective, well-tolerated, and economical treatment strategy for healthy adults who report fatigue

STRENGTHS

- The study is a double-blind randomized placebo-controlled trial
- The vitamin D study medication and the placebo were manufactured to have identical appearance, taste and smell
- The study had an adequate number of participants
- The study dose was appropriate

LIMITATIONS

- Extensive exclusion criteria makes the study results not very generalizable
- The participants were all enrolled from a very small subset of the general population
- Participants were instructed not to take vitamin D preparations or other vitamins and supplements during the entire study period but they may have taken some anyway either knowingly or unknowingly

- The study duration was not very long and only included one dose
- There was the potential for lots of confounding variables that were not controlled for
- The study used very subjective measures (a self-report survey) for the primary outcome

CONCLUSION

- Although the study does present some positive results with the use of vitamin D, more studies should be done before its use should be too heavily recommended for fatigue. Specifically, a longer study duration is needed, a method should be used for fatigue other than just self-report survey, and the patient population should better represent the general population.

Reference: Nowak A, Boesch L, Andres E, et al. Effect of vitamin D3 on self-perceived fatigue: A double-blind randomized placebo-controlled trial. *Medicine.* 2016. 95:e5353.

Alyssa Ruberto, MBA, Doctor of Pharmacy Candidate
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