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VITAMIN D EFFICACY AND SAFETY IN RELATION TO BONE HEALTH: A REVIEW

Dr Ajay Pant*

*Department of Medical,
Teerthanker Mahaveer University, Moradabad, Uttar Pradesh, INDIA
Email id: drajay.pant@gmail.com

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ABSTRACT

The goal of this assessment report was to compile information on the efficacy and safety of vitamin D from food and UV radiation in terms of bone healthcare outcomes at all stages of life. The objectives were to discover knowledge gaps for the scientific community as well as areas that needed further study. We conducted a tiered selection procedure with synthesis of findings from 167 included studies after conducting a thorough literature review across various databases. We considered a wide range of outcomes in our analysis (eg, falls, bone mineral density, fractures, and adverse events). This report includes a summary of the key results as well as an explanation of the methodology. We also go through places where the data isn't conclusive, as well as methodological problems we ran across. We discovered mixed evidence of a link between serum 25-hydroxyvitamin D [25(OH)D] level and bone mass content in babies, as well as reasonable evidence of a link between bone mineral content and density in older children and adults. The evidence for a link between blood 25(OH)D level and some patient outcomes (fractures, performance measures) in menopause women and older men was mixed, while the evidence for a link with accidents was fair. We discovered strong evidence of a beneficial impact of vitamin D–fortified meals on 25(OH)D levels. The information showing vitamin D's role in preventing falls and fractures was mixed. We found reasonable evidence that people tolerated vitamin D at dosages beyond current dietary guideline consumption levels, but no information on the link between greater vitamin D dosages and long-term effects.

KEYWORDS: *Adults, Bone Health, Efficacy, Serum, Vitamin D.*

1. INTRODUCTION

Fractures caused by osteoporosis are a significant socioeconomic burden. Annually, 1.5 to 2 million event fractures occur in the United States, with direct medical expenditures of osteoporosis ranging from $13.7 to $20.3 billion. Fractures are expected to become more common over the next several decades as the world's aging population. For the prevention of osteoporotic fractures, guidelines suggest sufficient calcium and vitamin D diets, as well as anti - resorptive medicines. The circulating 25-hydroxyvitamin D [25(OH)D] was designated as the useful indicator of vitamin D status in the 1997 US Institute of Medicine report on dietary reference intakes for calcium and related minerals. The combined contribution of cutaneous production and food consumption, including vitamin D supplementation, is reflected in circulating 25(OH)D concentrations. Due to a lack of scientific evidence, the Institute of Medicine was unable to determine estimated average needs on which to base recommended daily allowances for vitamin D, therefore it supplied acceptable intake levels instead. Vitamin D consumption should be sufficient to meet specified criteria of adequacy, such as the prevention of rickets or osteomalacia in all members of a healthy community. The tolerated upper intake level (the maximum amount of daily nutrient intake that is unlikely to cause adverse health effects in nearly all people in the general population) of vitamin D

for people 1 year and older (or 1000 IU per day for babies) is based on inadequate data. Although many assays are available for measuring blood 25(OH)D levels, they have methodological limitations. Vitamin D status assessments are difficult due to a lack of standardization of the various analytic methods of measuring circulating 25(OH)D concentrations, resulting in both interassay and interlaboratory variability, as well as a lack of reference standards preparations and readjusting materials.(1)

A comprehensive evaluation of the data on the effectiveness and safety of vitamin D in connection to bone health outcomes was sponsored by the National Institutes of Health and the Agency for Healthcare Research and Quality.(2) The purpose of this study was to educate the scientific community about knowledge gaps and limitations in current evidence so that future study priorities might be identified. Another aim was to help the review's sponsors in producing information for healthcare professionals and the general public on the usage of vitamin D supplements. The main results of the study are summarized in this article, as well as the difficulties we faced when performing a systematic assessment of vitamin D nutritional forms and UV sources.(3)

2. DISCUSSION

1. Systematic Review process:

A methodical review of research findings reduces bias by giving a repeatable, complete overview of the entire body of data, as opposed to a narrative review that concentrates on the outcomes of individual studies. As a consequence, a systematic review may improve the chances of making the best choice possible based on all available information. Systematic reviews are often used to assess medical treatments and diagnostic tests, but they are less commonly used to evaluate nutritional supplements. The team from the University of Ottawa's Evidence-based Management Center analyzed the literature to answer five important questions: 1) Is there a link between circulating 25(OH)D concentrations and bone health outcomes in different age groups (infants, children, women of reproductive age, and elderly men and women)? 2) Does fortification of foods, sun exposure, or vitamin D prescription alter circulation 25(OH)D levels? 3) What is the scientific evidence for the impact of vitamin D supplementation on bone mineral density (BMD) and fracture or fall risk? 4) Is a certain amount of sun exposure enough to maintain appropriate vitamin D levels while reducing the risk of nonmelanoma skin cancer and melanoma? 5) Does exceeding current recommended vitamin D consumption levels cause toxicity (e.g., hypercalcemia, hypercalciuria, or nephrolithiasis)? During the review process, an independent panel of vitamin D content experts (nutrition scientists, biochemists, and medical specialists) as well as representatives from the National Institutes of Health and the Agency for Healthcare Research and Quality offered input and assisted to refine the key questions. To answer the five main issues, the researchers devised an analytic framework that highlighted connections between study populations, various vitamin D sources (dietary consumption, supplements, and ultraviolet B radiation), and pertinent outcomes represented in (Figure 1).(2)

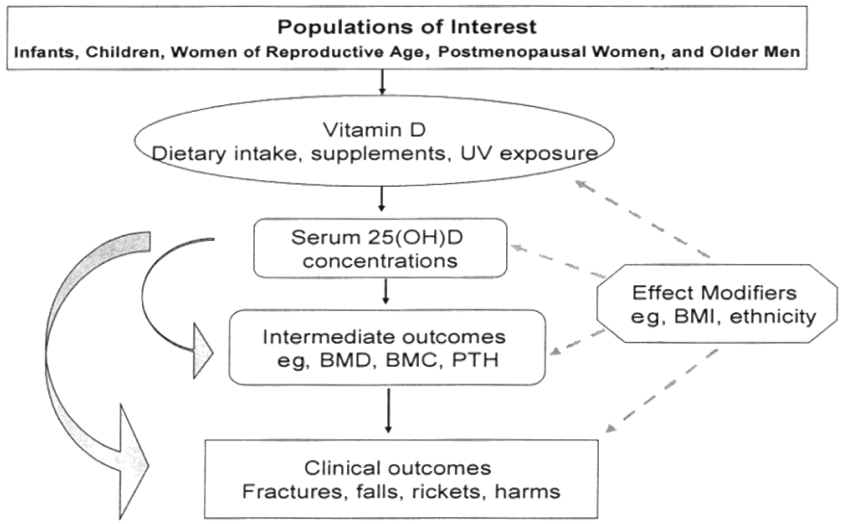

Figure 1: Analytic framework for evidence review on vitamin D. UV, ultraviolet; 25(OH)D, 25-hydroxyvitamin D; BMD, bone mineral density; BMC, bone mineral content; PTH, parathyroid hormone; BMI, body mass index(2).

2. Search strategy and eligibility criteria:

MEDLINE (National Library of Medicine, Bethesda, MD; 1966 to June Week 3, 2006), EMBASE (2002 to 2006 week 25), CINAHL (1982 to June Week 4, 2006), AMED (1985 to June 2006), Biological Abstracts (1990 to February 2005), and The Cochrane Central Register of Controlled Trials were all started searching without language restrictions. The researchers limited the studies they chose to those that were published in English and included human subjects. To avoid bias and concentrate on the greatest amount of proof for issues, the team utilized randomized controlled trials (RCTs) wherever feasible. For questions 2-5 the researchers only considered studies that compared vitamin D2 or D3 (with or without calcium) to a control group. Due to a lack of RCTs in this area, the team expanded the inclusion criteria for question 1 to include prospective cohort, casecontrol, and before-and-after studies that discussed the relationship between serum 25(OH)D densities and bone health outcomes, particularly in infants and children, and limited ask 4 to existing reviews(4).

3. Study selection:

The team used a three-step method to evaluate the search results. One examiner went through all of the bibliographic data, including the title and abstract. Second, two reviewers used the complete report to filter possibly relevant records and applied stringent qualifying criteria. Any disagreements between the two independent reviewers were addressed by consensus or judgment by the third reviewer. Third, the team evaluated research for study design and classified them according to their relevance to each topic(5).

4. Data extraction:

Study and demographic parameters, type of 25(OH)D test, vitamin D intervention (type, dosage, frequency of administration), co-interventions, reported confounders or variables, and pertinent bone health outcomes were all abstracted by two reviewers. The team came to an agreement to settle their disagreements(6).

5. Evaluation of the study's quality:

The Jadad 5-point scale, including evaluates randomization, double-blinding, and the description of dropouts and withdrawals, was used to assess the quality of the randomized trials included in the review. Using the Schulz approach, the team evaluated the adequacy of allocation concealment

as sufficient, inadequate, or uncertain. Figure 1 represented the analytic framework for vitamin D evidence assessment. For observational studies, the researchers used a Figure 1 to assess methodological quality (poor, fair, or good). UV is for ultraviolet; 25(OH)D stands for 25-hydroxyvitamin D; BMD stands for bone mineral density; BMC stands for bone mineral content; PTH stands for parathyroid hormone; BMI stands for body mass index. Cranney and others are grading system modified from Harris et al. The number, quality, and consistency of findings were used to determine the overall degree of evidence (good, fair, or inconsistent).(2)

6. Data synthesis:

Because of the many assays (radioimmunoassay, enzyme-linked immunoassay, competitive binding protein assay, and HPLC) utilized in the trials, the researchers did not try to calibrate blood 25(OH)D concentrations across investigations. In the meta-analyses, the researchers utilized the difference in means between treatment groups for continuous outcomes [e.g. BMD and serum 25(OH)D]. The difference in the percentage growth in BMD from baseline was utilized to pool the BMD findings. Absolute changes in 25(OH)D were utilized to pool 25(OH)D. For binary events, such as falls, combined odds ratios were calculated using the number of individuals who experienced the event. The researchers used a weighted mean technique to perform meta-analyses. To get combined estimates of weighted mean differences and associated standard errors, the researchers first utilized the fixed effects model. The degree of multi - oriented across studies was determined using chi-square (Q) and I2 statistics. The researchers utilized a random-effects approach to generate pooled estimates across the trials where study variability was substantial. The I2 statistic was used to assess the degree of statistical heterogeneity. If the Forest plot, or I2 statistic, revealed a high level of variation, the researchers looked into it further using subgroup, sensitivity, and meta-regression analyses, if needed.(7)

5. Summary of research needs:

In response to the information gaps we discovered throughout the study, we highlighted numerous research needs:

- Agreed-upon goals for vitamin D sufficiency and deficiency to assist determine vitamin D adequacy, researcher employed a range of intermediate and clinical outcomes. The vitamin D research community must agree on which results are useful indicators of vitamin D deficiency at all life stages.
- Validated 25(OH) D concentration tests in the lab Because of the imprecision of the 25(OH)D assays, we had difficulties establishing limits of circulating 25(OH)D levels compatible with optimum bone health. Standard reference preparations for 25(OH) D assay validation should be developed by the National Institute of Standards and Technology and the Office of Dietary Supplements. Researchers will be able to use these materials to determine the 25(OH) D concentrations that are linked with sufficient vitamin D status throughout the life cycle.
- Information on the health of babies, children, and teenagers' bones postmenopausal women and older males were included in majority of the higher-quality studies. To establish sufficient and safe vitamin D intakes, we require high-quality research trials evaluating the relationship between vitamin D status and bone health outcomes in babies, children, and adolescents(8).
- Vitamin D's dose-response relationship in babies, children, pregnant and nursing women Few studies have looked at how incremental multivitamin doses from fortified foods and supplements affect vitamin D and calcium absorption in babies, pregnant women, and women of reproductive age. More study is needed in this area.

- Data on effectiveness and side effects in vitamin D studies are consistently reported. To assist the synthesis of the data on vitamin D, we require uniform reporting of outcomes, including hazards.
- In High-quality research in underrepresented areas we discovered limited studies on vitamin D's effects on African Americans, Hispanics, and Native Americans. As a result, research examining the relationship between particular 25(OH)D concentrations and bone health outcomes in these groups are needed(2).
- A better knowledge of the factors that influence vitamin D's impact Another area where further study is needed is the lack of data on the influence of effect modifiers (such as latitude, season, ethnicity, and BMI) on 25(OH)D concentrations and bone health outcomes(8).
- Vitamin D reactions to UV light exposure, as well as the dangers and advantages we need a comprehensive assessment of the research on sun exposure to assess the advantages and risks of UV radiation levels that offer sufficient vitamin D photosynthesis for bone health(9)(10).

3. CONCLUSION

Our comprehensive evidence analysis of relevant literature on the safety and efficacy of vitamin D from nutraceuticals and ultraviolet B exposure to light on bone health outcomes at various stages of life was presented. We looked at the results of 167 papers that matched our criteria for study design. Vitamin D supplementation raises 25(OH)D levels and promotes bone health, according to some research. However, we identified few or mostly low-quality studies, conflicting findings, or insufficient information for several outcomes and groups of interest, such as babies, adolescents, and pregnancy or lactating mothers. To close the research gaps we found, the vitamin D group needs to reach an agreement on endpoints for vitamin D suitability and insufficiency, behavior more high-quality trials of vitamin D's effect on bone strength in a wider variety of populations, and report all important outcomes (including adverse events) in a complete and accurate format.

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