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Subphysiologic Doses of Vitamin D are Subtherapeutic: Comment on the Study by The Record Trial Group

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Dear Editor,
Based on recently published research, it is clear that the study by The Record Trial Group [1] on vitamin D and calcium in the prevention of fractures suffered from at least four important shortcomings which negatively skewed their results.

First, and most important, the dose of vitamin D used in their study (800 IU/d) is subphysiologic and would therefore not be expected to produce a clinically meaningful effect. The physiologic requirement for vitamin D was determined scientifically in a recent study by Heaney and colleagues [2], who showed that healthy men utilize 3,000 to 5,000 IU of cholecalciferol per day, and several recent clinical trials have been published documenting the safety and effectiveness of administering vitamin D in physiologic doses of at least 4,000 IU per day.[3-5] In fact, studies have shown a dose-response relationship with vitamin D supplementation [6], and low doses (e.g., 600 IU) are clearly less effective than higher doses in the physiologic range (e.g., 4,000 IU).[5] It is important to note that the commonly used dose of vitamin D at 800 IU per day was not determined scientifically; rather this amount was determined arbitrarily before sufficient scientific methodology was available.[2,7] Given that the commonly recommended daily intake of vitamin D in the range of 200-800 IU is not sufficient for maintaining adequate serum levels of vitamin D [8], it is therefore incumbent upon modern researchers and clinicians to use doses of vitamin D that are consistent with the physiologic requirement as established in current research.

Second, the authors recognize that patient compliance in their study population was quite poor. This poor compliance obviously contributed to the purported lack of treatment efficacy.

Third, and consistent with recent data published elsewhere [8], virtually all of their patients were still vitamin D deficient at the end of one year of treatment, thereby affirming the inadequacy of the treatment dose. Vitamin D deficiency is common in industrialized nations, particularly those of northern latitudes [9-11], including the UK, where this study was performed. By modern criteria for serum vitamin D levels [12], virtually all of the patients in this study were vitamin D deficient at the beginning of the study, and the insufficient treatment dose of 800 IU/d failed to correct this deficiency even after 1 year of treatment. Given that vitamin D levels must be raised to approximately 40 ng/mL (100 nmol/L) in order to maximally reduce parathyroid hormone levels and bone resorption [13,14], supplementation that does not accomplish the goal of raising serum vitamin D levels into the optimal physiologic range cannot be considered adequate therapy.[12]

Fourth, and finally, there is reason to question the bioavailability of their vitamin D3 supplement, as the authors note that their dose-response was generally lower than that seen in other studies. Bioavailability is a prerequisite for treatment efficacy, and the elderly have higher likeliness of comorbid conditions that impair digestion and absorption of nutrients. Specifically, it is well documented that vitamin D absorption is decreased in elderly patients compared to younger controls [15,16], and this is complicated by an age-related reduction in renal calcitriol production [17,18] and intestinal vitamin D receptors [19], thereby further impairing vitamin D metabolism and calcium absorption. Since emulsification of fat soluble vitamins is required for their absorption [20], and since pre-emulsification of nutrients has been shown to increase absorption and dose-responsiveness of the fat-soluble nutrient coenzyme Q [21, 22], it seems apparent that attention to the form (not merely the dose) of nutrient supplementation is clinically important, particularly when working with elderly patients.

These shortcomings, when combined, could have lead to an additive or synergistic reduction in treatment potency that skewed their results toward a conclusion of inefficacy. In order to produce more meaningful results in clinical trials, our group published guidelines [12] recommending that future studies 1) ensure patient compliance, 2) use physiologic doses of vitamin D (e.g., 4,000 IU per day), and 3) ensure that serum levels are raised to a minimum of 40 ng/mL (100 nmol/L), since levels below this threshold are associated with increased parathyroid hormone levels, increased bone resorption, and recalcitrance to bone-building interventions.[23,24]

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