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Using findings from observational studies to guide vitamin D randomized controlled trials

In their meta-analysis of 25-hydroxyvitamin D [25(OH)D] levels of fallers and nonfallers, Annweiler and Beauchet [1] found that people with levels <20 ng mL^{-1} had the greatest risk of falling, whereas the finding for levels <10 or <30 ng mL^{-1} were not significant. Therefore, levels from 20 to 30 ng mL^{-1} were optimal for reducing risk of falls. However, the odds ratio (OR) for those with levels <10 ng mL^{-1} was 1.23 [95% confidence interval (CI), 0.94–1.60], so with more studies, the OR might be statistically significant. The OR for people with levels <30 ng mL^{-1} was 0.95 (95% CI, 0.81–1.11), which is reasonable; however, this result could be affected by those who started vitamin D supplementation late in life because of a physician's concern about bone health, as mentioned in [1].

Other studies have developed 25(OH)D level–health outcome relations from meta-analyses for such conditions as cardiovascular disease [2] and diabetes mellitus [3], as well as for parathyroid hormone disorders (PTH) [4]. Some evidence indicates that PTH has health effects independent of vitamin D [5]. Although relations for disease outcomes are limited by the small number of study cases, Valcour *et al.* [4] reported the relation for PTH from the records of 313 000 cases. The relation shows that PTH decreases with increasing 25(OH)D level out to 75 ng mL^{-1}. PTH is also higher at any value of 25(OH)D level at older ages: for 25 ng mL^{-1}, PTH for those younger than 20 years is 25 pg mL^{-1}, rising to 48 pg mL^{-1} for those older than 60 years. Thus, participant age may also affect results of vitamin D supplementation.

Figure 1 shows 25(OH)D level–health outcome relations for breast and colorectal cancer [6], cardiovascular disease [2], diabetes mellitus [3], and PTH for those >60 years of age [4]. The values for each relation were scaled from the original graphs so that they agree near 10 ng mL^{-1}. The agreement between the relations for the various diseases is excellent, suggesting that there may be a nearly universal 25(OH)D level–chronic disease

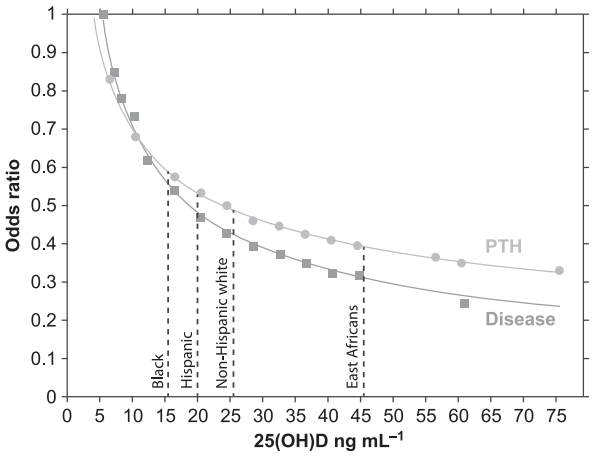

Fig. 1 *Breast and colorectal cancer, cardiovascular disease, diabetes risk and parathyroid hormone disorders vs. 25(OH)D levels [2–4, 6]. Mean serum 25(OH)D levels for black, Hispanic, non-Hispanic white [7] and traditionally living East Africans [8] are indicated.*

outcome relation. However, the relation for PTH lies somewhat above the other relations. Also shown in the figure are mean 25(OH)D levels for black, Hispanic, non-Hispanic white Americans [7] and traditionally living populations in East Africa [8], suggesting that most people can expect better health outcomes by increasing 25(OH)D levels.

A meta-analysis of vitamin D randomized controlled trials (RCTs) and fall prevention for elderly people found that only 800 and 1000 IU per day of vitamin D resulted in significant inverse correlation with falls [9]. Although many of those studies were conducted on people in nursing homes, who would be expected to have lower 25(OH)D levels, that analysis did not indicate that 25(OH)D levels were measured either at time of enrolment or after supplementation. A study in Finland found that those living in nursing homes had a mean value of 16 ng mL^{-1} [10]. According to the plot of expected risk of 25(OH)D level per 1000 IU per day of vitamin D_3 with respect to starting 25(OH)D level, supplementation of 1000 IU per day for those with

levels of 16 ng mL^{-1} would yield a final value of 26 ng mL^{-1} [11].

However, vitamin D RCTs with community-dwelling individuals generally do not find significant benefits associated with vitamin D supplementation for cardiovascular disease, cancer, total fractures or hip fracture [12]. In community-dwelling populations, elderly people in 2000–2008 had mean 25(OH)D levels of 26 ng mL^{-1} in Asia/Pacific, 21 ng mL^{-1} in Europe and 29 ng mL^{-1} in North America [13]. Thus, most elderly community-dwelling people already have 25(OH)D levels in the range where increasing the levels would be expected to reduce adverse health outcomes by perhaps 15% [12]. In fact, a 15% reduction in all-cause mortality rate was the estimate for raising 25(OH)D levels from 22 to 44 ng mL^{-1} [14].

An important implication of this study is that blood 25(OH)D level–health outcome relations from observational studies should guide the design of vitamin D RCTs that evaluate risk of falling. Two recent papers have made this point [15, 16], indicating that vitamin D RCTs have generally been based on the pharmaceutical drug model: assuming no other source of the agent and that a linear dose–response relation is present. However, other sources of vitamin D exist—ultraviolet-B irradiance and oral intake—and the 25(OH)D level–health outcome relations are not linear. These authors recommend that RCT design:

- starts with the best estimate of the 25(OH)D level–health outcome relation of interest,
- seeks to enrol people with 25(OH)D levels near the low end of the relation,
- measures 25(OH)D levels before accepting people into the study,
- supplements with enough vitamin D_3 to raise levels to the relation's plateau and then
- measures 25(OH)D levels during the study.

Heaney [16] also recommends optimizing participant nutritional status with respect to all related nutrients. The journal literature includes vitamin D RCTs conducted on both supposedly healthy community-dwelling people with 'normal' 25(OH)D levels and those with low 25(OH)D levels. One example is on risk of respiratory infections. A study in New Zealand with a mean serum 25(OH)D level of 29 ng mL^{-1} at baseline and increased to 48 ng mL^{-1} found no significant effect on upper respiratory tract infections [17]. However, a study in Mongolia of children with a mean baseline 25(OH)D level of 7 ng mL^{-1} supplemented with 300 IU per day of vitamin D_3 found a rate ratio of 0.52 (95% CI, 0.31–0.89) for acute respiratory infection [18].

For cancer, a reanalysis of the 7-year Women's Health Initiative RCT involving 400 IU per day of vitamin D_3 and 1500 mg per day of calcium found that women 'who were not taking personal calcium or vitamin D supplements at randomization, CaD [calcium plus vitamin D supplementation] significantly decreased the risk of total, breast and invasive breast cancers by 14–20% and nonsignificantly reduced the risk of colorectal cancer by 17%' [19]. No significant effects for cancer were evident for the other participants. This finding is consistent with the 25(OH)D level–cancer incidence rate relation for breast and colorectal cancer from observational studies [6]. According to these relations, supplementing people with a baseline 25(OH)D level of 16 ng mL^{-1} with 400 IU per day would increase the level to 20 ng mL^{-1} and reduce the OR of cancer by 11%, whereas the same approach for those with levels of 30 ng mL^{-1} would increase the 25(OH)D level to 33 ng mL^{-1} and reduce the OR by 7%. Calcium supplementation also reduces risk of cancer [20, 21], which modifies the effect of vitamin D_3 plus calcium supplementation compared with vitamin D_3 alone.

Many recommendations on vitamin D supplementation and 25(OH)D levels are based on both observational studies and RCTs. The American Geriatrics Society's recommendations on vitamin D for prevention of falls are particularly germane. The society reviewed the evidence as of 2009; of the 10 primary sources, six looked at blood levels of 25(OH)D, PTH or 1,25-dihydroxyvitamin D, whereas four involved supplemental vitamin D, sometimes with calcium [22]. The Endocrine Society made recommendations based on a combination of observational studies on skeletal effects related to 25(OH)D levels and vitamin D RCTs investigating both skeletal effects and 25(OH)D levels [23]. For nonskeletal effects, the society noted that because of the paucity of vitamin D RCTs, it relied on meta-analyses of observational studies of outcomes

related to 25(OH)D levels. Other groups, such as an *ad hoc* vitamin D experts group [24] and the 550 health professionals attending a vitamin D conference in Warsaw in October 2012 [25], made recommendations that relied much more heavily on observational studies than RCTs. Two other factors support the recommendations of vitamin D: many of the molecular mechanisms of vitamin D action are well known [25, 26], and vitamin D supplementation is associated with few adverse effects.

Thus, although one implication of the Annweiler and Beauchet [1] study is that their 'findings participate in further elucidating the profile of ideal target populations, which is the first step to provide effective guidelines on the proper use of vitamin D supplements for fall prevention in the elderly,' the larger implication is that researchers can use observational studies of health outcomes with respect to 25(OH)D levels to formulate vitamin D guidelines—at least until high-quality vitamin D RCTs are available.

Conflict of interest

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