Vitamin D supplementation and risk of infectious disease: no easy answers¹⁻³

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The effect of sunlight on infectious disease has intrigued scientists and clinicians for more than a century (1). In 1903, Niels Finsen won the Nobel Prize for his work on the beneficial effect of UV radiation on lupus vulgaris (cutaneous tuberculosis). This discovery contributed to the development of mountain clinics where sunlight was used to treat patients with respiratory tuberculosis. Heliotherapy (helios = sun) was largely abandoned during the 1940s and 1950s after the introduction of effective antituberculous medications. Several decades then passed with relatively little attention to the antiinfective properties of sunlight and, more specifically, vitamin D. Although many people speculated about the potential role of vitamin D on risk of acute respiratory infection (ARI), the hypothesis received more attention after the publication of a 2006 review article by Cannell et al (2), who suggested a major role for vitamin D in influenza risk. Over the past decade, many observational studies have examined this possibility, including a national study that found an inverse association between serum concentrations of 25-hydroxyvitamin D [25(OH)D], the best marker of vitamin D status, and recent ARI in each of the 4 seasons (3), thereby refuting the idea that the association between 25(OH)D and ARI risk was simply due to confounding by winter season.

Over the past 5 y, dozens of randomized controlled trials (RCTs) have examined the connection between vitamin D status and infection risk, with most focusing on ARI (1). Although some RCTs showed strong evidence of benefit (4), others showed no benefit whatsoever (5). Indeed, recent meta-analyses of the results from published trials also have reached contradictory conclusions, with one group reporting that vitamin D supplementation lowers risk of ARI (6), whereas another found no association (7). The 2011 Institute of Medicine report (8) was completed before most of the currently available RCTs, but already it was apparent that the association was more complicated than suggested by the observational studies. Along those lines, the more recent RCT results suggest likely interactions of the vitamin D–ARI association by baseline vitamin D status (ie, vitamin D–deficient individuals receive more benefit than those with normal concentrations) and possibly greater benefit for subgroups that are at higher risk of ARIs, such as young children, older adults, or individuals with immune defects that increase their ARI risk. With regard to other acute infectious diseases (eg, urinary tract infection, cellulitis, sepsis, and many other types of infections), sparse data are available (1).

In this issue of the Journal, Tran et al (9) report on the effect of vitamin D supplementation on antibiotic use in adults. Briefly, the investigators performed a post hoc analysis of data from the pilot study (n = 644) for D-Health, a recently funded RCT of vitamin D supplementation and health in Australia. The pilot RCT enrolled subjects aged 60–84 y and had 3 arms: placebo, 30,000 IU vitamin D₃ monthly, and 60,000 IU vitamin D₃ monthly. The primary outcome of this post hoc analysis was antibiotics prescribed during the intervention period, as identified by linkage with pharmacy records through the Australian national health insurance program. Although those in the higher-dose group had a nonsignificant 28% lower risk of having antibiotics prescribed at least once, stratification by age showed no benefit for those aged <70 y but a significant 47% risk reduction for those aged ≥70 y. The P value for interaction by age was 0.1.

The trial has several strengths, including a double-blinded, placebo-controlled RCT design; use of both low and high doses of vitamin D₃; 9- to 12-mo duration; and use of a “harder” outcome (antibiotic prescription) rather than self-reported infection—although the reliability of any self-reported outcomes would presumably be similar in the randomly assigned groups. A limitation of many pilot studies, this one included, is low statistical power. Another limitation is the post hoc analysis and the potential for type 1 error. Along those lines, the interaction P value (0.1) does not satisfy the traditional criteria for “statistical significance” (P < 0.05). Nevertheless, given the myriad effects of vitamin D on the immune system (10) and ongoing uncertainty about the effect of vitamin D on risk of infectious diseases, we commend the authors for publishing their interesting results.

References

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⁠⁴ Abbreviations used: ARI, acute respiratory infection; IPD, individual patient data; RCT, randomized controlled trial; ViDA, Vitamin D Assessment; VITAL, VTamIn D and Omega-3 Trial; 25(OH)D, 25-hydroxyvitamin D.

Several large RCTs are underway that are likely to shed light on this issue before the D-Health project is done. For example, the Vitamin D Assessment (ViDA) trial in New Zealand has randomly assigned >5100 older adults (aged 50–84 y) to receive vitamin D$_3$ 100,000 IU monthly and will examine prevention of respiratory infections as a secondary aim (ACTRN12611000402943). Likewise, the VITamin D and OmegA-3 Trial (VITAL) in the United States has randomly assigned >25,000 older adults (aged ≥50 y) to receive vitamin D$_3$ (2000 IU daily) or omega-3 fatty acids (1 g daily) using a 2x2 factorial design (NCT01169259). VITAL Infection is an ancillary study within VITAL that focuses on the effect of the 2 interventions on a variety of infections. Results from these ongoing large RCTs should be available in 2016 and 2017, respectively. These large RCTs, and others like them, will be able to directly test the effect of vitamin D on infectious disease risk, and more specifically, examine possible interactions by age, baseline 25(OH)D concentrations, and other variables.

In the meantime, an individual patient data (IPD) meta-analysis could provide helpful information in that it allows examination of a variety of potential interactions, including age group, baseline 25(OH)D concentration, and vitamin D dosing regimen. At a minimum, an IPD meta-analysis can provide guidance to researchers on what questions show completely null results (based on current data) and for which additional trials are not needed. Under the leadership of Adrian Martineau, more than a dozen key investigators from published RCTs of vitamin D supplementation have agreed to participate in an IPD meta-analysis focused on ARI and related outcomes (eg, asthma exacerbations). Early results should be available in mid-2014. With regard to the many other infectious diseases that might be affected by vitamin D status, moderate-sized RCTs (and IPD meta-analyses) are urgently needed. Such studies could provide interim answers (and research guidance) while we await the completion of the much larger, population-based trials.

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REFERENCES