Vitamin D dosing for infectious and immune disorders

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The most natural way that humans get vitamin D into their body is through exposure to sunlight. If one is at the equator in the summer without sunscreen, human skin will produce approximately 10 000 IU of vitamin D over one hour, a testament to the incredible reserve that human skin has to translate ultraviolet light B (UVB) exposure into vitamin D3 levels in serum.

However, modern culture has made sun exposure an inefficient transducer of vitamin D. First, humans spend upwards of 90% of their time indoors and, when outside, have clothes and sunscreen on, both of which reduce the exposure to UVB radiation and, consequently, the production of vitamin D in the skin. Finally, in countries such as the UK, that are far north of the equator, for at least 6 months of the year, there is significantly less UVB radiation that reaches the earth's surface given the larger solar zenith angle of the sun's rays with respect to the earth's surface.[1] We are a long way from where modern humans originated, 10 000 years ago, naked, at the equator and outdoors 100% of the time.

Thus, to get enough vitamin D, humans must rely on supplementation of their diet to attain appropriate intake. The fact that we have this dual mechanism is testament to the critical biological role that vitamin D plays in human immunity and physiology. This dietary supplementation has been used since the middle of the 18th century when cod-liver oil was regularly used to treat rickets. Unfortunately, we have got away from cod-liver oil, and there is now considerable controversy as to how much vitamin D people should take for immune function. Things are clearer for bone health. We only need to target a serum level of 20–30 ng/mL, or 50–75 nmol/L, to prevent rickets. Bone and Ca metabolism are clearly controlled by serum levels of vitamin D and parathyroid hormone, for example, via an endocrine feedback system. Even at these modest levels, a considerable percentage of the adult UK population (between 40% and 80% depending on age group) and the world's population (greater than 40% in many countries) is deficient, for example, below 20 ng/mL or 50 nmol/L.[2 3]

While the likely optimal level for bone health is known, the central question is what level is needed for prevention of infection and immune health? Here is where things get murky. There is a suggestion from an observational study by Sabetta *et al*,[4] where 25 OHD (25 hydroxy D) was measured monthly, that maintaining a serum level of at least 38 ng/mL is needed for adequate protection from acute respiratory infections. In addition, since most immune cells have the biochemical apparatus to make the active form of vitamin D, for example, 1,25 dihydroxy D (1,25 OHD) and there is diffusion of vitamin D3 (the precursor molecule) and 25 OHD into the tissues it is likely that the levels needed are not well reflected by the levels in the serum and that higher serum levels are required for immune health. We believe that this level should be in the range of 40–60 ng/mL or 100–150 nmol/L.

What are the implications of needing this higher level for immune health? There are several. The first implication is that serum levels are a poor reflection of tissue levels and reliance on 25 OHD levels as the sole index of normal vitamin D status is probably insufficient and misleading.[5] The second implication is that while levels for bone health are well established, the levels needed for infectious and immune health are not as clear. People frequently cite the level of 30 ng/mL or 75 nmol/L as the upper range of normal for immune health but this is completely unproven. What does appear to be true is that you don't begin to get suppression of parathyroid hormone until the serum level is 40 ng/mL suggesting that this is the true lower limit of normal, not 30 ng/mL.[6] Now niche populations such as the Masai in Africa and professional surfers are among the few people in the world with adequate sun exposure to get normal serum levels of vitamin D and they have levels of 40–60 ng/mL (100–150 nmol/L) a range thought by many, including us, to be more appropriate for infectious and immune health than current recommendations.[7 8] If we are correct then the level of human vitamin D deficiency is truly astounding as 99+% of the world's population would be deficient and substantially so. Given these assumptions, clinical trials are critical to prove the appropriate dosing of vitamin D; observational studies are unable to do this given the massive levels of insufficiency worldwide.

All this serves as important background in considering the recent ViDiFlu trial in this issue of *Thorax*.[9] In this trial the investigators used a clever block randomisation scheme to attempt to prevent influenza outcomes with vitamin D supplementation. In addition to the usual daily dose of 400 IU in the elderly they employed bolus dosing every 2 months with 2.4 mg, for example, 96 000 IU. Being in the treatment group was actually associated with an increased risk of upper respiratory tract infection (URI) and increased duration of URI symptoms.

Clearly the vitamin D didn't work to reduce infections so what went wrong here? The first problem was that 25 hydroxy vitamin D levels were the only measure of treatment efficacy and the measurements were taken at 2 months and 12 months at trough times, for example, well after the last bolus dose. The mean 2-month level was 65.5 nmoles below the target level of 75 nmoles/L and certainly well below 100 nmoles/L. The 12-month level was 85.3 75 nmoles/L so, above 75 nmoles/L, but still well below 100 nmoles/L. So it looks as if the dosing was too low to achieve adequate tissue levels, and certainly well below the level that Sabetta *et al*[4] had previously shown to be effective in preventing acute respiratory infections. In addition, as noted by the authors, the whole concept of bolus dosing of vitamin D is problematic. Intermittent bolus dosing with long lag times (greater than 3–4 weeks) leads to wide swings in circulating levels of 25 OHD, which in turn leads to dips in tissue levels of 1,25 dihydroxy D, leading to a relative excess of the catabolic enzyme 24 hydroxylase.[10] This mechanism has also been suggested to be operating in elevating the risk for some cancers due to wide fluctuations in circulating vitamin D levels. Given the adverse effects associated with vitamin D supplementation seen in this trial, a mechanism similar to this is likely to be operating. In support of this idea other bolus dosing trials have been null,[11–13] while trials using regular oral dosing even in modest levels have been protective.[14 15]

In summary vitamin D has very complex biochemistry and in designing trials using it as a treatment modality we

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should avoid wide swings in tissue levels by infrequent bolus dosing, not rely on intermittent serum monitoring and try to attain a consistent immune protective level of 100–150 nmoles/L (40–60 ng/mL). If we do these things we will see some positive results and benefit our patients.

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