When Is a U-Curve Actually a J-Curve? Is It Really Too Much of a Good Thing?

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Dror et al (1) present an interesting analysis of the relationship between measured 25-hydroxyvitamin D (25-OH D) levels and mortality and acute coronary syndrome outcomes in a community-based health maintenance organization in Israel over a 54-month period in this issue of the *JCEM*.

They report a U-shaped relationship around an optimal 25-OH D level of 20–36 ng/ml (50–90 nmol/L). Mortality and acute coronary syndrome events were progressively more frequent with lower 25-OH D [adjusted hazard ratio (HR), 1.26 for 25-OH D of 10–20 ng/ml (25–50 nmol/L), and 1.91 for values < 10 ng/ml (<25 nmol/L)]. However, they also noted a modest increase in risk [adjusted HR, 1.13 with higher 25-OH D values > 36 ng/ml (>90 nmol/L)]. This is really a J-shaped relationship.

There was no evidence of a dose–response relationship at the higher levels of 25-OH D [virtually the same apparent adjusted HR for 36–40 ng/ml (90–100 nmol/L); 40–44 ng/ml (100–110 nmol/L), and > 44 ng/ml (>110 nmol/L)]. The lack of an apparent dose relationship at higher levels of 25-OH D may relate to the small numbers in this range and the very few with the highest levels (not directly stated, but apparently less than 1% of the total population measured).

Dror et al (1) interpreted their data to indicate that care should be taken with vitamin D supplementation without careful observation of the 25-OH D levels before initiation and during follow-up. At one level, this conclusion is rational in that it suggests that "treatment' should be based on evidence of need, even for a vitamin and even in generally healthy individuals. At another level, it seriously overstates the possible causative nature of the observed relationships in either direction. Without randomized controlled trials, it is not appropriate to confidently attribute positive outcomes to raising 25-OH D levels into an optimal range or negative outcomes to exceeding optimal levels.

The data of Dror et al (1) on low 25-OH D are supported by much data that associate low 25-OH D levels with poor health outcomes (2), including in acute intensive care environments (3, 4). Importantly, based on the frequency of the 25-OH D values and the adjusted HRs, the attributable risk for mortality and acute coronary syndrome events is 31.8% for 25-OH D values below 20 ng/ml (<50 nmol/L) vs 0.55% for 25-OH D values above 36 ng/ml (>90 nmol/L). Thus, if one were to take these attributable risks at face value, it seems that the ratio of risk to benefit of indiscriminant vitamin D supplementation in an unscreened population would exceed 50:1.

A strength of this study is that virtually all members of the population in Israel are in one health fund or the other; that is the way in which population health care funding is distributed. Hence, the sample represents a true population sample. On the other hand, although the measured individuals represented approximately 33% of the total health fund membership over the age of 45 years, those expected to have lower 25-OH D levels, eg, current smokers and the overweight or obese, were under-represented in the sample. It is not known how including such individuals would have influenced the findings.

One challenging aspect of the Dror et al study (1), given the observational nature of this analysis, is that these tests

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For article see page 2160

Abbreviations: HR, hazard ratio; 25-OH D, 25-hydroxyvitamin D.

were taken and the outcomes measured over a 54-month period. Hence, some people would have been observed for a relatively short period after the measurement, whereas others would have had more than 4 years of follow-up. This could be important because the health care providers that ordered these tests would have seen and possibly acted on the results. Considering the uncertain causality of the 25-OH D and mortality outcomes, it is unlikely but not impossible that treatment given based on the 25-OH D result could have contributed to the adverse outcomes. This possibility is not implausible given that high oral doses of vitamin D (500 000 IU) were associated with more falls and more fractures in a randomized controlled Australian study (5, 6). However, as presented, there are no data on treatments given after the 25-OH D results were available. Nor for that matter nor are there any data presented by Dror et al (1) on relevant physiological outcomes, such as serum calcium or 24-hour urine calcium excretion.

Despite some of these challenges, this study adds to the body of evidence of adverse outcomes associated with low vitamin D levels, but the precise mechanisms remain elusive. The evidence of an adverse effect of relatively high levels is modest and, as such, is of uncertain mechanism or significance. The authors reasonably suggest that caution should be exercised with vitamin D therapy, and it seems rational to advocate using 25-OH D measurements to guide treatment. However, there is no doubt that there is a serious need for adequately powered randomized controlled trials of efficacy and safety of vitamin D treatment in individuals with low (and normal) 25-OH D levels. These are required to inform rational clinical practice.

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