

Supplementary material for reviewers of our submission, Tony Woo et al:

Since we would expect reviewers of our submission to question the rationale for vitamin D use, in light of a recent study by Tuohimaa et al, that high vit D may increase risk of prostate cancer we attach a recently submitted Letter to editor regarding Tuohimaa P, Tenkanen L, Ahonen M et al. Both high and low levels of blood vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case-control study in the Nordic countries. *Int.J.Cancer 2004;108:104-8.*

Enzyme kinetics hypothesis to explain the U-shaped risk curve for prostate cancer vs 25-hydroxyvitamin D in Nordic countries.

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To the editor: Tuohimaa et al have shown quite convincingly that there is a U-shaped curve for prostate cancer risk vs 25(OH)D levels in Norway, Finland, and Sweden (1). To explain this, they proposed a mechanism involving excessive catabolism of 1,25(OH)2D within prostate by 24-hydroxylase induced by 25(OH)D (1). However, this does not explain the paradox of why the minimal risk of prostate cancer would occur with 25(OH)D levels that are *average* for Sweden (1), a country suffering what may be the *highest* rate of prostate cancer mortality in the world (2).

I would like to offer a hypothesis that refines the explanation of Tuohimaa et al (1). Basic to this hypothesis is the fact that the enzymes of the vitamin D system function below their Km values *in vivo* (3;4). Thus, when 25(OH)D levels fall, the ratio between 25(OH)D-1-hydroxylase and 25(OH)D-24-hydroxylase must go up to reestablish set-point levels of 1,25(OH)2D produced within tissues like the prostate. Endocrine production of 1,25(OH)2D by the kidney can reestablish the setpoint quickly because there, the enzymes are regulated by PTH, calcium, and phosphate (4;5). However, at the prostate, adaptation to a decline in 25(OH)D is probably much slower, because so far as we know, the net output of 1,25(OH)2D is determined only by 25(OH)D supply, and by the self-adjusting balance between 25(OH)D-1-hydroxylase and 25(OH)D-24-hydroxylase.

When 25(OH)D is increased acutely in the rat, renal production of 1,25(OH)2D transiently overshoots its setpoint (3;4). It follows from this

that, if 25(OH)D declines, there is a similar phase where 1,25(OH)2D undershoots its setpoint. Figure 1 illustrates this hypothesis. Winter at high latitudes produces a prolonged, gradual decline in 25(OH)D levels, and during this decline, autocrine 1,25(OH)2D cannot be maintained at its long-term setpoint.

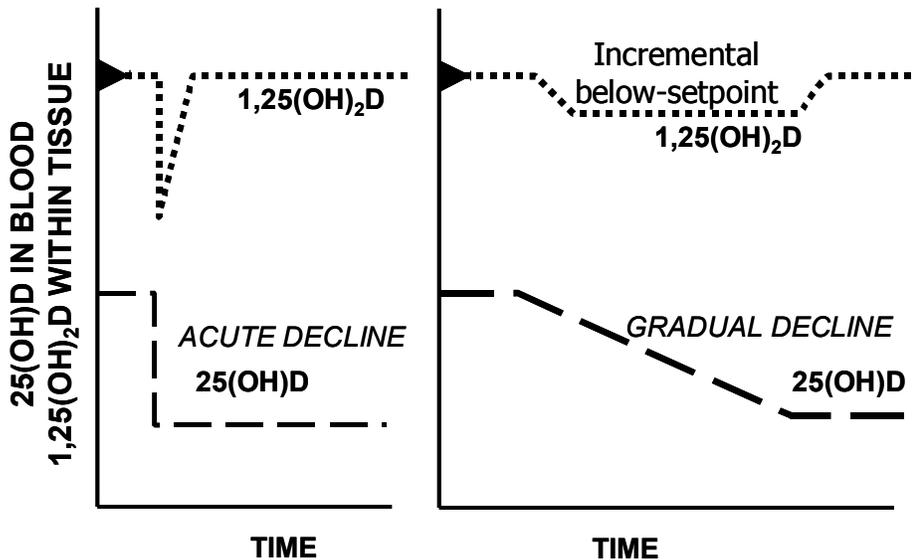
According to this hypothesis, high 25(OH)D concentrations are not problematic *per se*. Instead, it is the process of declining 25(OH)D concentrations that contributes to increased risk of prostate cancer. Tuohimaa et al reported large seasonal differences in 25(OH)D levels (1). Those men having the highest summertime 25(OH)D levels should be expected to exhibit the greatest decline during the winter phase of each year. Men with higher summer 25(OH)D levels would suffer a more severe sub-set-point phase of prostate-generated 1,25(OH)2D. Annual cycles of prolonged incremental inadequacy of tissue 1,25(OH)2D levels could increase risk prostate cancer, and account for the U-shaped risk relationship.

This hypothesis predicts that the U-shaped curve of prostate cancer risk is distinct to high latitudes. It predicts that in regions where average 25(OH)D concentrations are higher and more constant throughout the year, greater risk of prostate cancer is associated only with low 25(OH)D levels. Humans are optimized through evolution to be a tropical species. Annual cycles of fluctuating 25(OH)D concentrations are not physiologic and may increase risk of prostate cancer.

FIGURE LEGEND

Figure 1. **Hypothesized effect of a decline in circulating 25(OH)D (dash lines) on tissue levels of 1,25(OH)₂D (dotted lines).** Since physiologic 25(OH)D concentrations are below the Km values of 1-hydroxylase, any decrease in 25(OH)D concentration results in fall in 1,25(OH)₂D below its setpoint (black arrows) until the ratio of 1-hydroxylase to 24-hydroxylase increases to compensate. With a prolonged decline, as during long winters, prostate-generated 1,25(OH)₂D cannot fully return to its setpoint until the 25(OH)D stops falling.

Figure



Reference List

1. Tuohimaa P, Tenkanen L, Ahonen M et al. Both high and low levels of blood vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case-control study in the Nordic countries. *Int.J.Cancer* 2004;108:104-8.
2. Hsing AW, Tsao L, Devesa SS. International trends and patterns of prostate cancer incidence and mortality. *Int.J.Cancer* 2000;85:60-7.
3. Vieth R, McCarten K, Norwich KH. Role of 25-hydroxyvitamin D3 dose in determining rat 1,25-dihydroxyvitamin D3 production. *American Journal of Physiology* 1990;258:E780-9.
4. Vieth, R. and Milojevic, S. Moderate vitamin D3 supplementation lowers serum 1,25-dihydroxyvitamin D3 in rats. *Nutrition Research* 15(5), 725-731. 1995.
5. Vieth R, Milojevic S, Peltekova V. Improved cholecalciferol nutrition in rats is noncalcemic, suppresses parathyroid hormone and increases responsiveness to 1, 25-dihydroxycholecalciferol. *J.Nutr.* 2000;130:578-84.