

Comment on “Vitamin D discovery outpaces FDA decision making”

“Before you let the sun in, make sure it wipes its shoes”

Dylan Thomas, Under Milk Wood. 1954

Sir,

It is always wise to consider evidence from points of view other than those that are current ‘received wisdom’ so that we can see clearly what we are really looking at. Thus, the above review is of considerable interest.⁽¹⁾ The author postulates that circulating hormonal [activated] vitamin D (calcitriol) concentration is more important than circulating 25-hydroxyvitamin D [25-(OH)D] in the determination of tissue functions that are modulated by vitamin D. He also appears to suggest that changes in circulating 25-hydroxy vitamin D reflect changes in calcitriol formation and uptake rather than availability of vitamin D and that circulating calcitriol concentration tells us about vitamin D effectiveness. This would indeed be the case if all tissues depended on uptake of calcitriol from the circulation for their supplies of hormonal vitamin D. However, many tissues express the hydroxylase activating vitamin D and several have been confirmed as producers of calcitriol *in situ*.^(2–4) Such tissues must use circulating 25-(OH)D, the substrate for activation by 25-hydroxyvitamin D 1-alpha-hydroxylase. Thus, for example, in the placenta, calcitriol is produced in large amounts from early in pregnancy with increases in circulating maternal calcitriol and reductions in maternal circulating 25-(OH)D.⁽⁴⁾ However, to suggest that all variation on serum 25-(OH)D concentrations in different disease processes reflects changes in local tissue vitamin D activation to the exclusion of variations due to the amount of vitamin D in the body would be to ignore the massive changes in serum 25-(OH)D seen within hours of exposure to UVB, without any changes in circulating calcitriol⁽⁵⁾ and would not explain the remarkable seasonal variations in serum 25-(OH)D seen with variation in available effective UVB from sunlight, with variations in dietary intake of vitamin D and with supplement use. In Sweden for example, in a group of 116 women in the winter, an average serum 25(OH)D of 69 nmol/l was accounted for by the following: (1) daily intake of normally fortified Swedish foods, 6.2 nmol/l, (2) three fish meals/week, 25.5 nmol/l, (3) regular vitamin supplement use, 11.0 nmol/l and (4) a vacation in the sun within the last 6 months, 14.5 nmol/l, which leaves 11.8 nmol/l of 25-(OH)D to be accounted for

the balance between incoming vitamin D and the amount of 25-(OH)D being consumed by local vitamin D activating tissues.^(6,7) In addition, however much ultraviolet B effective for induction of vitamin D synthesis [effUVB] one is exposed to, vitamin D toxicity does not develop because of feed-back mechanisms in the skin itself.⁽⁸⁾ Similarly, feed-back mechanisms ensure that circulating calcitriol is virtually unchanged in the face of reductions in serum 25-(OH)D in the circulation until there is clinically obvious vitamin D deficiency with bone disease such as rickets or osteomalacia when calcitriol does eventually fall, though even then, in some case, serum calcitriol is found to be increased.⁽⁹⁾ These findings challenge the argument that vitamin D modulation of tissue function depends predominantly on circulating calcitriol and explain why vitamin D repletion continues to be judged at present by circulating concentrations of the storage adduct, 25-(OH)D, acting as it does as the substrate for local tissue activation throughout the body and not just in the kidney. In support of this position, it is well known that measurement of circulating calcitriol [hormonally active 1,25dihydroxyvitamin D] is unhelpful in the assessment of vitamin D repletion since its concentrations are normally so tightly regulated across a wide range of concentrations of 25-(OH)D.⁽¹⁰⁾ Finally, the fact that vitamin D activation has been demonstrated in several of the extrarenal human tissues known to express specific vitamin D activating 1-alpha hydroxylase supports the view that assessment of substrate availability of vitamin D, as reflected by serum 25-(OH)D, is likely to be of importance in the assessment of vitamin D repletion in humans.

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