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Vitamin D: the alternative hypothesis

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In the spirit of Dr. Barry Kramer's remarks, I am going to discuss the vitamin D secosteroids from the perspective of molecular biology and recent research pointing to immunosuppressive effects of vitamin D supplementation.

The Tufts report under consideration repeatedly alludes to two vitamin D metabolites: 25-D and 1,25-D. As the report states, 1,25-D is the biologically active form, and it seems most researchers would agree that 25-D is the inactive form. There is a significant difference though between a molecule which is an inert substance - in other words, totally inactive - and one which interferes with transcriptional activity, and it is this distinction which I would like to spend my time discussing.

To review, some have called the VDR the "gatekeeper of the innate immune system." The VDR is now known to transcribe nearly a thousand genes including a number of key antimicrobial peptides including the beta-defensins and cathelicidin. The VDR is normally activated by its native ligand, the active form of vitamin D, 1,25-D.

But if the Vitamin D Receptor plays a vital role in the innate immune response, what explains the statement by Arnson and Shoenfeld, the latter of whom is editor-in-chief of *Autoimmunity Reviews*: "Vitamin D has multiple immunosuppressant properties"?

Our group has found an answer that differs from the conventional view and has the advantage of explaining a wider range of real-world observations.

In a recent paper, Professor Tony Norman implies that 25-D does not bind the Vitamin D Receptor.[1]

The paper I recently published in *Autoimmunity Reviews*, based on our *in silico* and clinical data, shows that, in contrast to Dr. Norman's finding, 25-D *is* able to bind the VDR. We have found that both 1,25-D and 25-D, which

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[1] As Dr. Norman let us know afterwards, this characterization of his view is not up to date with his current thinking. If pressed, however, we could probably find other prominent vitamin D researchers who would argue this.

are superimposed in this figure, and have nearly identical structures, have high affinities for the VDR, with the Kd of 1,25-D being 8.48 and that of 25-D being 8.36.

But – and this is my most important point – we have found that 25-D, lacking *this* one additional hydroxyl group, cannot activate the VDR. Instead, as its concentration builds, it actually inactivates VDR expression.

This poses a problem, because if 25-D slows VDR activity, we're facing the possibility that the form of vitamin D that would be elevated by increasing the level of dietary supplementation stifles rather than activates genetic transcription and immune function.

As the report suggests, the evidence for vitamin D's efficacy in chronic disease is mixed. But some studies do seem to show a benefit. For those studies, we would argue that what researchers perceive as this benefit is instead temporary palliation due to reduced VDR activity with the higher the dose of vitamin D administered, the higher the palliation observed.

Indeed, the secosteroid 25-D may exert palliation on the innate immune system not unlike the way corticosteroids exert palliation on the adaptive immune system.

So is it possible then that supplemental vitamin D is now perceived as a wonder substance by some simply because it effectively palliates the inflammation associated with diseases across the board? If so, this would certainly explain why its effects are most noticeable in the short-term and why efficacy often diminishes in the long-term.

For example, a 2000 study published in the *Archives of Internal Medicine,* found that five patients confined to wheelchairs with severe weakness and fatigue were able to walk after being administered 300,000 IU's of vitamin D over a period of six weeks. Yet no follow-up study was ever published on the group, suggesting that their ability to walk was only a temporary phenomenon. This is the type of reaction we would only expect to see from a powerful immunosuppressant, an immunosuppressant that offers short-term inflammatory relief but is actually harmful over longer periods of time as it causes the activity of the immune system to become increasingly compromised.

Indeed there are several studies that show that vitamin D's negative effects are most noticeable over the long-term. Studies that are more likely to reflect long term effects found higher rates of brain lesions, allergies, atopy,

and kidney stones in patients who were studied for periods up to 30 years after beginning to take vitamin D. These papers are cited in my recent *Autoimmunity Review*.

Another important consideration has not received adequate attention. The push by some to raise the DRI to historically high levels is grounded in the assertion that an increasing proportion of the American public is deficient in 25-D, the metabolite we have found is immunosuppressive.

More specifically, since a low level of 25-D is now commonly seen in patients with a variety of diagnoses, it has been assumed that diminished levels of the secosteroid are contributing to ill health.

Yet, the alternate hypothesis must be considered - that the low levels of 25-D observed in patients with chronic disease could just as easily be a *result* rather than a *cause* of the inflammatory disease process.

Our research suggests that this is the case. Indeed, we have found that 1,25-D tends to rise in patients with chronic disease and that these high levels of 1,25-D are able to downregulate through the PXR nuclear receptor the amount of pre-vitamin D converted into 25-D, leading to lower levels of 25-D. I describe this finding further in my paper.

So are we really facing an epidemic of vitamin D "deficiency" or are we simply beginning to note more signs of an imminent epidemic of chronic disease – an epidemic which would be exacerbated by increasing the amount of vitamin D added to our food supply?