Autoimmunity Research Foundation

Rethinking vitamin D deficiency

Amy Proal

My colleague Professor Trevor Marshall wanted to be here today, but could not come because he is in China presenting a genetic basis for the VDR's actions in cancer at a biotech conference in Dalian.

This is a figure from his recent paper in *Bioessays* - a transcriptional description explaining how all the enzymes and metabolites are expressed from the human genome. As we know, the different forms of vitamin D are actually secosteroids with activity in many type 1 nuclear receptors. For example, my own recent paper in *Annals of New York Academy of Sciences* examines the effect of vitamin D on the thyroid, androgen, and other nuclear receptors.

This diagram allows one to see our group's depiction of how the actions of the various vitamin D metabolites are interrelated. As you can see, the PXR, the VDR and p300 transcription factors all play a vital role in homeostasis of the vitamin D metabolites. This model depicts about eight feedback and feedforward pathways regulating vitamin D homeostasis and there may be more. Clearly, this is not a first order mass action metabolism that would allow for a simple vitamin in, benefit out model.

Instead, the extremely delicate control of numerous homeostatic pathways is telling. So we need to seriously consider, at the molecular level, exactly how this homeostasis shifted when the food chain was supplemented with unnaturally high levels of vitamin D. As Paul Albert just described, it is possible that 25-D, which our molecular and clinical data shows binds and deactivates the VDR, exerting its perceived beneficial effects by working as a powerful immunosuppressant. In this sense it may be the closest thing we have to a "natural prednisone" - a substance that allows for temporary palliation and inflammatory relief but at the risk of the population's long-term health. We must keep in mind that there is a difference between feeling better and getting better. And we must keep in mind that the American population is getting sicker and sicker.

Now some of you may be thinking, "Well that's a just a model and where is the clinical evidence?" That evidence lies in the results of a clinical trial my organization, Autoimmunity Research Foundation, has been conducting over

the past seven years for patients with serious inflammatory disease. Central to the trial is the use of a VDR agonist that allows patients to restore innate immune function. But supplemental vitamin D was not suitable as a VDR agonist because, in addition to slowing VDR activity, it targets so many of the other nuclear hormone receptors, as discussed in my Annals paper. Instead we use a special dosing of the ARB olmesartan which agonizes the VDR more directly. And what we see is that patients do not recover until their 25-D falls below an immunosuppressive threshold of 20 ng/ml.

1,100 subjects have been through our cohort in the first seven years, of which 750 are still fully reporting. Data showing that a majority of our study subjects have experienced symptomatic resolution and/or disease reversal from a variety of autoimmune diagnoses, was presented by Capt. Tom Perez at the 2008 International Congress on Autoimmunity in Portugal, where Prof Marshall chaired a special session on vitamin D in Autoimmune Disease.

Next month clinical trials are starting at West China Hospital. The hospital has 4,600 beds, is the largest clinical center in the world, and is the Chinese center for the Cochrane Collaboration in evidence-based medicine. The trial is intended to validate the results from our initial study in a controlled phase 3 clinical environment. We're moving fast on this trial and data should be coming out over the next few months and years. We expect the first data from the study to be published at the International Congress on Autoimmunity in Ljubljana next May.

So does this 25-D level that we've identified as immunosuppressive make sense when viewed alongside data from healthy populations where the food supply has not been supplemented? Such studies are hard to find since, for example, all the powdered milk Europe ships to 3rd world countries has been fortified with vitamin D for decades.

A study on healthy Bangladeshi women in a remote community found that 80% of the women had a level of 25-D under 16 ng/ml. Another study showed that healthy Chinese infants were born with levels of 25-D between only 5- 14 ng/ml, yet none of these children developed Rickets. And China. to this day, still does not supplement their food supply with any vitamin D whatsoever. Therefore the studies we're doing at WHC will bring in good clean data on an unsupplemented population.

Returning to the studies I just mentioned, all subjects were OK, healthy - and yet in America they would almost certainly be readily diagnosed with severe vitamin D deficiency and be heavily supplemented. But the problem may not be deficiency but instead a misunderstanding of how the different forms of vitamin D are regulated by the body both in heath and disease.

Even breast milk has been criticized as being too low in "vitamin D" - but it seems unlikely that evolution would have allowed this situation to arise.

It's time to take a step back and look at this issue with fresh eyes. If we are correct, and 25-D acts in a manner opposite to 1,25-D, then supplemental vitamin D must be viewed in a new light.

But it's been very challenging to summarize the totality of our research in a five minute talk. I'd love to chat with you a discuss more details of our work and any questions that you may have.