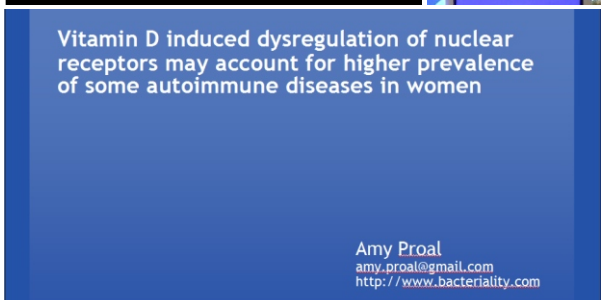
Vitamin D induced dysregulation of nuclear receptors may account for higher prevalence of some autoimmune diseases in women

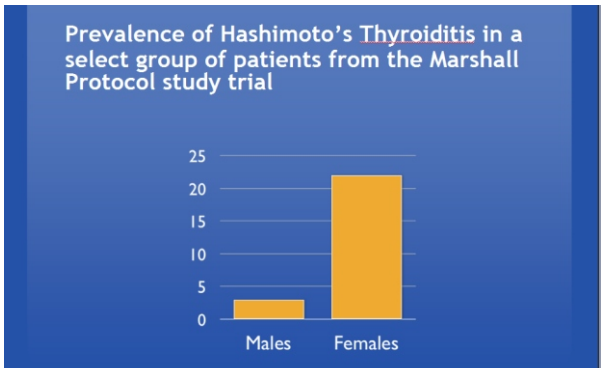
PRESENTED BY AMY PROAL
[http://vimeo.com/1788640]



[00:00:19 SLIDE 1]

Trevor Marshall: Thank you. Next, Amy Proal from Georgetown University is going to discuss why vitamin D induced dysregulation of nuclear receptors may account for higher prevalence of some autoimmune diseases in women. Thank you Amy.

Amy Proal: First of all, I would also like to thank the conference organizers for giving me the opportunity to speak. Thank you very much. I am going to examine why autoimmune diseases such as Hashimoto's Thyroditis are much more likely to occur in women than in men, especially during the childbearing years.



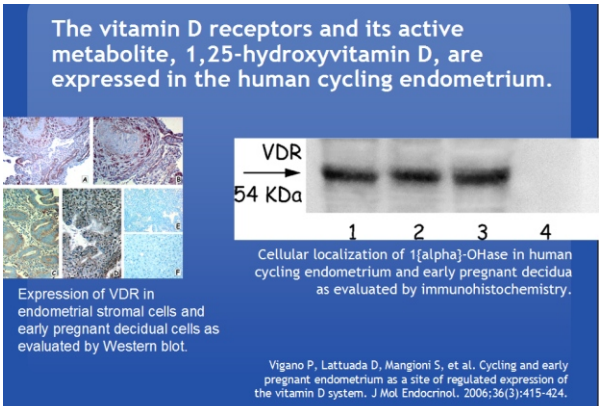
[00:01:28 SLIDE 2]

Prevalence of Hashimoto's Thyroiditis... (slide 2)

For example, in the study discussed by Prof. Marshall in which both sexes are allowed to participate equally, out of 104 subjects surveyed, 24 have Hashimoto's, but only 3 of them are men.

What might be going on?

One obvious difference between the sexes is that they express hormones at different levels. Furthermore, as Professor Marshall and other researchers have shown, the Vitamin D Nuclear Receptor (VDR) controls important components of innate immune response, particularly, transcription of the betaDefensin and cathelecidin antimicrobial peptides.[1)]



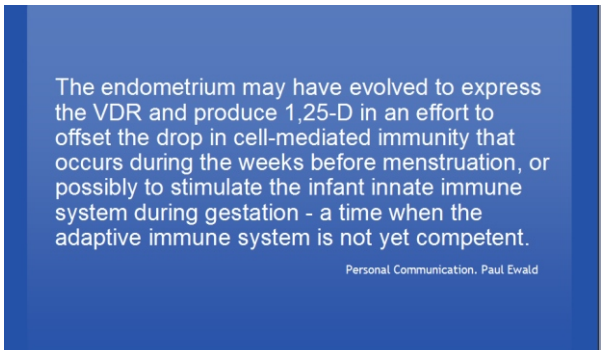
[00:02:10 SLIDE 3]

The vitamin D receptors... (slide 3)

Vigano's recent work has confirmed [in a 1978 study showing] that the active vitamin D metabolite 1,25 hydroxyvitamin-D (1,25-D) is produced in the human cycling endometrium.[2)] He also showed, using Western blot analysis and immunohistochemistry, that both cycling and early pregnant endometrial cells express the VDR, which is activated by 1,25-D. Finally, he showed a 40% increase in 1,25-D production in the early pregnant decidua.

1) Marshall TG. Vitamin D discovery outpaces FDA decision making. Bioessays 30, p. 173-82 (2008 Feb).

2) Viganò P, Lattuada D, Mangioni S, Ermellino L, Vignali M, Caporizzo E, Panina-Bordignon P, Besozzi M, Di Blasio AM. Cycling and early pregnant endometrium as a site of regulated expression of the vitamin D system. J Mol Endocrinol 36, p. 415-24 (2006 Jun).

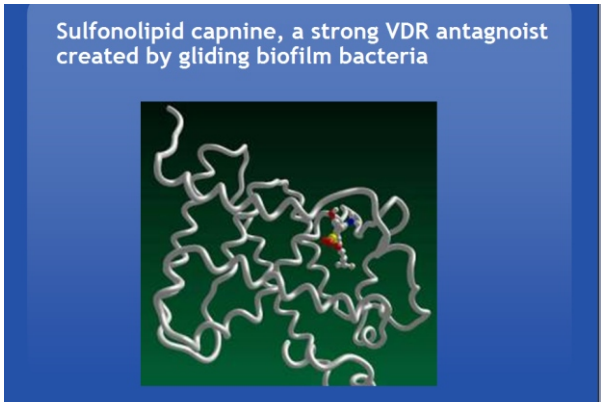


[00:02:41 SLIDE 4]

The endometrium... (slide 4)

The endometrium may have evolved to express the VDR and produce 1,25-D in an effort to stimulate the infant innate immune system during gestation, or perhaps, to offset the drop in cell mediated immunity that occurs during the weeks before menstruation.

But increasing evidence indicates that at some point in the history of man, a microbiota composed largely of intraphagocytic and biofilm bacteria evolved a way to take advantage of the innate immune response by creating ligands that dysregulate VDR activity.

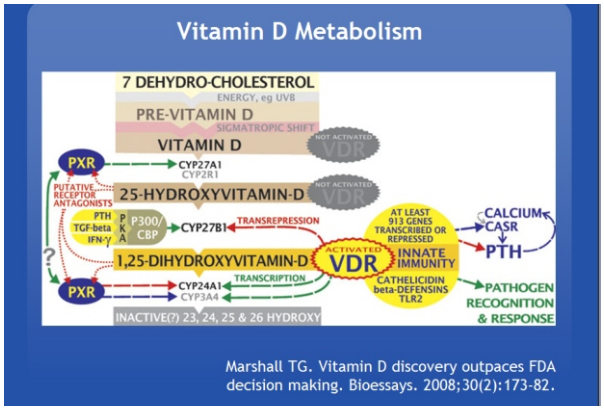


[00:03:15 SLIDE 5]

Sulfonolipid capnine... (slide 5)

For example, Prof. Marshall has shown that the sulfonolipid capnine, which is created by gliding biofilm bacteria, is a strong VDR antagonist. I should also add that we refer to this microbiota as the Th1 pathogens, since their presence is associated with elevated interferon gamma.

Since the Th1 pathogens are able to dysregulate the VDR, they have perverted what was intended to be a protective environment during pregnancy and menstruation into one that allows them to flourish. When the ligands they create disable the VDR, expression of betaDefensin and cathelecidin is curtailed rather than activated.

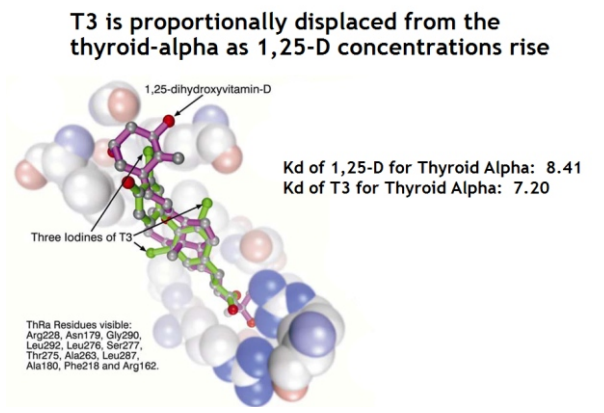


[00:03:57 SLIDE 6]

Vitamin D Metabolism (slide 6)

And unfortunately, VDR dysregulation also has other effects that allow the Th1 pathogens to further proliferate. You can see from this figure that when active, the VDR transcribes CYP24A1, an enzyme that breaks 1,25-D down into the inactive vitamin D metabolites.

But what happens if the VDR is dysregulated by the Th1 pathogens? Under such conditions CYP24A1 is no longer transcribed and 1,25-D is able to rise without a feedback system to keep it in check.

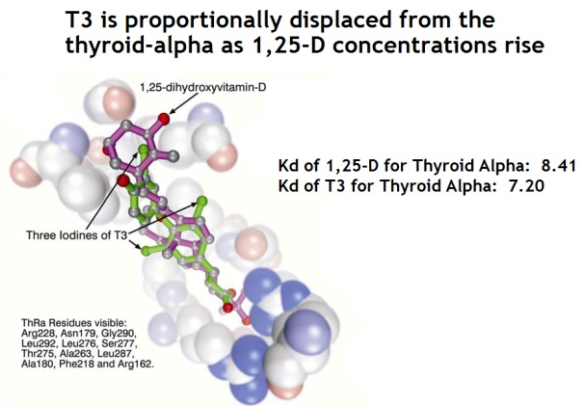


[00:04:34 VIDEO/SLIDE 7]

T3 is proportionally... (slide 7)

Marshall's in-silico modeling has shown that 1,25-D also has a strong affinity for the body's other nuclear receptors, suggesting that at high levels it can interfere with their activity. Since I'm discussing Thyroiditis let's take a look at the effects of elevated 1,25-D on thyroid alpha.

Here is the emulation of the alpha thyroid nuclear receptor, ThRa. Marshall has shown that 1,25-D has a very high affinity for ThRa - a Kd of 8.41. Normally levels of T3, which has a Kd 7.20 for ThRa, keep 1,25-D out of the binding pocket, but as 1,25-D rises due to

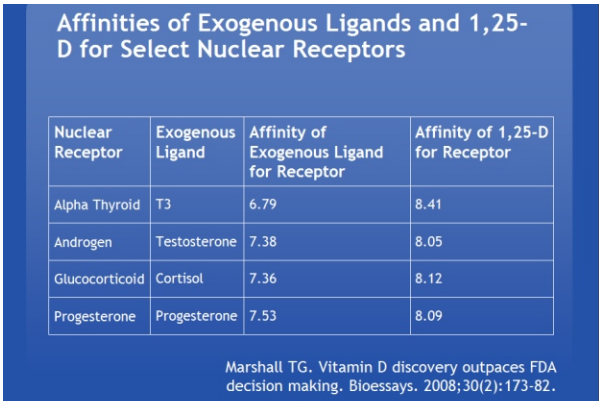


[00:04:34 VIDEO/SLIDE 7, continued]

VDR dysregulation, it starts to proportionately displace T3 and block transcription by thyroid alpha. The same thing happens with thyroid beta since 1,25-D has a Kd of 8.44 for the receptor.

So, when 1,25-D displaces T3, the genes with alpha thyroid promoters can no longer be transcribed. T3 is displaced, therefore the thyroid can not function properly, resulting in the phenomenon recently described as thyroid hormone resistance.

This may explain why increasing levels of thyroid hormone are necessary in order to keep 1,25-D out of ThRa as the disease progresses, a measure that is palliative but not curative. And since all the type 1 nuclear receptors work as a group, when transcription by ThRa is dysregulated, system wide gene transcription is also affected.



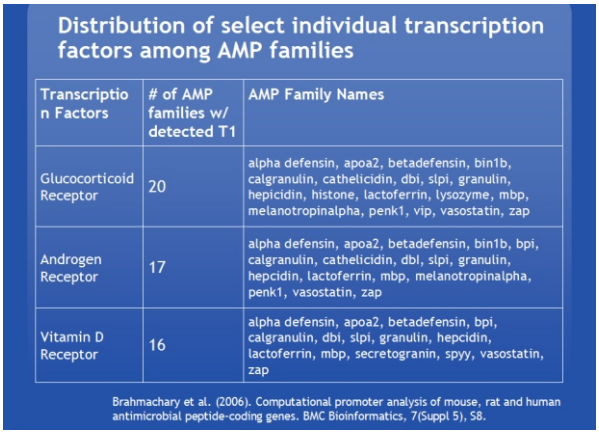
[00:06:11 SLIDE 8]

Affinities of Exogenous Ligands and 1,25-D... (slide 8)

And as I mentioned before, this same pattern is repeated when it comes to several of the body's other nuclear receptors.

For example, Marshall has shown that 1,25-D has a Kd of 8.05 for the Androgen receptor, and a Kd of 8.12 for the Glucocorticoid receptor. So elevated 1,25-D can displace cortisol and testosterone from their target receptors as well, resulting in an array of other hormonal imbalances.

An additional effect is also of importance. By disabling the nuclear receptors, 1,25-D also has detrimental effects on system-wide Anti Microbial Peptide (AMP) production.



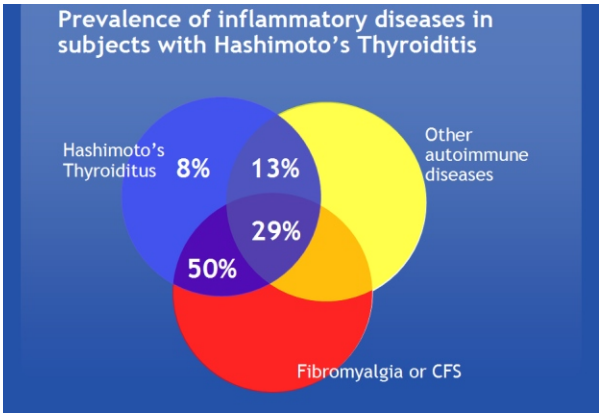
[00:06:49 SLIDE 9]

Distribution of select individual transcription... (slide 9)

Just as the VDR expresses betaDefensin and cathelecidin, other nuclear receptors also express AMPs. Take a look at this table which presents data taken from a recent analysis of AMP expression by Brahmachary. You can see that the Glucocorticoid, Androgen, and the Vitamin D Receptor seem to be in control of 20, 17, and 16 [respective] families of AMPs out of 22 analyzed.

So disabling the VDR with flow-on effects to glucocorticoid, thyroid, androgen, and other nuclear receptors delivers a knockout blow to the body's antimicrobial peptide production. Disabling the VDR and subsequently the AMPs is a very logical thing for pathogens to have done, so much so, that if such a survival mechanism were possible, it seems quite likely it would have evolved.

It comes as little surprise, then, that hormonal dysregulation is so intricately connected to autoimmune disease.



[00:07:53 SLIDE 10]

Prevalence of inflammatory diseases... (slide 10)

For example, you can see here that most of the patients with Hashimoto's analyzed by our study have also been diagnosed with other inflammatory or autoimmune diseases. In fact, only 8% of subjects with Hashimoto's have Hashimoto's alone.

We now have a pathway in the molecular biology showing how these apparently diverse physiological conditions can interact.

Essentially, VDR dysregulation, and the drop in AMP expression that it instigates, allow the Th1 pathogens that Marshall describes in autoimmune disease to spread with greater ease. Since patients are immunocompromised, they also pick up new Th1 pathogens including concomitant viral co-infections.

And what is more, since women have an extra site of VDR gene transcription — the endometrium — they express more VDRs than men. So the over-expression of the VDR in women may mean that, as they age, they are disproportionately affected by the drop in AMP expression associated with VDR dysregulation. So they end up with heavier bacterial loads and exhibit greater morbidity than their male counterparts.

This model may also explain why many women with autoimmune disease often find their symptoms escalate after pregnancy. Since 1,25-D rises by 40% in the early pregnant decidua, its ability to dysregulate the nuclear receptors, and the AMPs they express, is particularly prevalent during this time. So at least during the early stages of gestation, the Th1 pathogens are able to spread with exceptional ease.

Finally, I should also add that Marshall has shown that 25-hydroxyvitamin D (25-D), which is derived from supplemental vitamin D, is able to displace exogenous ligands from the nuclear receptors just as effectively as 1,25-D — marking a way in which it is able to suppress the innate immune response.

So it may indeed be possible that VDR dysregulation plays a significant role in the higher incidence of autoimmune disease observed among women, and that vitamin D supplementation could further account for the skew in incidence. Further research is needed.

Finally, I would like to also add one more thing. When it comes to correlating disease incidence with low levels of vitamin D, it is also incredibly important to consider the alternate hypothesis, which is that the low levels of vitamin D may not be causing the disease but may simply be a result of the disease process. So, a low level of vitamin D correlated with an illness may simply be an indicator that the disease process has taken an effect in that patient.

Thank you, and I appreciate your time.