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Three versions of vitamin D can activate the vitamin D receptor in some cells

/tom-weishaargmail-com/)



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Touhimaa P, Wang JH, Khan S, et al. Gene Expression Profiles in Human and Mouse Primary Cells Provide New Insights into the Differential Actions of Vitamin D Metabolites. *Plos One*. 2013;8(10):e75338. (<http://www.ncbi.nlm.nih.gov/pubmed/24116037>)

Nuclear receptors are found only in animal cells. They up- and down-regulate gene activity. In human cells there are 48 of them, one of which is activated, as we shall see, by various forms of vitamin D. Activating its nuclear receptor isn't the only metabolic effect of vitamin D, but it's clearly an important part of the mix.

The researchers set up this experiment using two types of cells. One type was from the human prostate gland and the other type was a modified mouse cell that couldn't produce the enzyme that converts the storage form of vitamin D, 25-hydroxyvitamin D [25(OH)D] into the classically active form, 1 α ,25(OH) $_2$ D.

Their idea was to split the cells into separate groups, give each group one of three different types of vitamin D, and determine what genes were turned on or off in response to the vitamin D. The mouse cells were included in the experiment to make sure that in the 25(OH)D group the results weren't actually 1 α ,25(OH) $_2$ D results because the cell had converted the one into the other. Since the mouse cells were unable to do the conversion, the researchers could be sure that any results they saw in that group were in fact due to 25(OH)D.

The third type of vitamin D the researchers included in the experiment was 24R,25 dihydroxy-vitamin D [24R,25(OH) $_2$ D]. This version is the first breakdown product of both 25(OH)D and 1 α ,25(OH) $_2$ D. The breakdown depends on an enzyme called 24-hydroxylase, which is made by a gene called CYP24A1. We'll get back to this gene in a moment.

In both the human and the mouse cells, the researchers found that all three versions of vitamin D activated the vitamin D receptor and, with some overlap, regulated different genes. In the human prostate cell, a total of 441 different genes were regulated up or down. Figure 1 shows the percentage of those 441 genes regulated by each version of vitamin D, as well as their overlap.

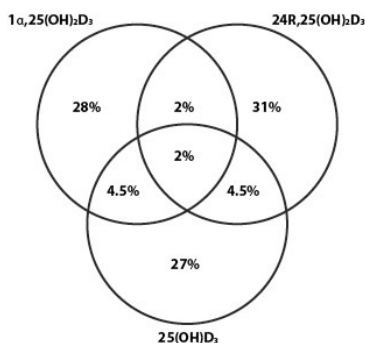


Figure 1. Percentages, showing overlap, of 441 genes regulated by different versions of vitamin D in the human prostate cell

One of the big surprises here is that the version of vitamin D that regulates the most genes (175) is 24R,25(OH) $_2$ D. This version of vitamin D had previously been shown to have some activity in vitamin D receptor knockout mice, but the authors say this is the first time it's been shown to activate the vitamin D receptor. The next big surprise is that the version of vitamin D that regulates the second-most number of genes (171) is 25(OH)D. What we heretofore considered the "activated" form of vitamin D, 1 α ,25(OH) $_2$ D, regulates a total of 164 genes in this particular kind of prostate cell.

One of the interesting findings is that the gene that both 25(OH)D and 1 α ,25(OH) $_2$ D up-regulated most strongly was CYP24A1 – the gene that creates the enzyme that converts these forms of vitamin D into 24R,25(OH) $_2$ D, beginning their own breakdown process. And 24R,25(OH) $_2$ D had no effect on this gene at all.

The researchers identified the types of genes that were being regulated in several different ways. One of these analyses looked into the network functions of genes exclusively regulated by a single version of vitamin D. 1 α ,25(OH) $_2$ D appears to be the version involved in cardiovascular, antimicrobial, and inflammatory health, while 25(OH)D and 24R,25(OH) $_2$ D seem more involved in cell-level processes which likely relate to cancer and neurological disease.

We have so much to learn.

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About Tom Weishaar

After a career writing about computers and personal finance, Tom Weishaar is a doctoral student in the health education program at Teachers College, Columbia University.

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8 Responses to *Three versions of vitamin D can activate the vitamin D receptor in some cells*



Rita and Misty says:

October 24, 2013 at 9:04 am (<https://www.vitamindcouncil.org/blog/three-versions-of-vitamin-d-can-activate-the-vitamin-d-receptor-in-some-cells/#comment-3330>)

Hey Tom—I enjoyed your article very much.

Taken from your article: “The next big surprise is that the version of vitamin D that regulates the second-most number of genes (171) is 25(OH)D.”

I’m certainly not a physician nor am I a research scientist, SO I apologize upfront if my thought process is inappropriate here....but in plain words: 25(OH)D is the prohormone produced in the liver after the liver breaks down vitamin D3...correct?

Think (just think) of the total disease burden to be lessened if folks maintained an optimal 25(OH)D level....

But, what is an optimal 25(OH)D level?

Is it hubris (really) to think that we require a level similar to our hunter/gatherer ancestors?

By the way, the graphics on this article are superb...and remind me of the passage...“it is easier for a camel to go through the eye of a needle than for a rich man to enter the kingdom of God....”

Yet, (and this is ironic), the universal monetary cost savings to society would be tremendous if the vitamin D deficiency pandemic were ended. And, dollars are required to better this physical world. Money is fundamentally a necessary tool to provide care to and for humanity. Little gets accomplished on good faith only...Certainly not the (expensive) research required to learn and understand about science...and this includes vitamin D research.

There is the Golden Rule: Those who have more are required to do more. In my opinion, how can our future generations forgive us for less?

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**Tom Weishaar** says:

October 24, 2013 at 2:02 pm (<https://www.vitamindcouncil.org/blog/three-versions-of-vitamin-d-can-activate-the-vitamin-d-receptor-in-some-cells/#comment-3331>)

(<https://www.vitamindcouncil.org/tag/vitamin-d-treatment>) (<https://www.vitamindcouncil.org/tag/vitar>

Rita – in the past I’ve referred to 25(OH)D as the “storage” form of vitamin D – it’s the form that’s measured in a vitamin D blood test, obviously. I’m not sure what to call it now, since in terms of the vitamin D receptor it appears to be as active as 1,25(OH)2D, which I’ve referred to in the past as the “activated” form. These findings may force us to come up with a new vocabulary.

**Rita and Misty** says:

October 24, 2013 at 2:26 pm (<https://www.vitamindcouncil.org/blog/three-versions-of-vitamin-d-can-activate-the-vitamin-d-receptor-in-some-cells/#comment-3332>)

I think we are living in an amazing time regarding vitamin D... I only hope that funding for necessary research will be available to help us answer those very important questions!

I also look forward to the 25(OH)D test being made standard on the blood panel...and I look forward to food fortification.

And of course, we need to work on sunshine regaining its appropriate place in all our lives....

Burning and sun sensitivity to me are signs of vitamin D deficiency.

**Ian** says:

October 24, 2013 at 6:19 pm (<https://www.vitamindcouncil.org/blog/three-versions-of-vitamin-d-can-activate-the-vitamin-d-receptor-in-some-cells/#comment-3334>)

24R,25 (OH)2D has been in the limelight before, not just as a breakdown product but as an active metabolite:

In this editorial:

<http://endo.endojournals.org/content/139/8/3371.full>
(<http://endo.endojournals.org/content/139/8/3371.full>)

and some articles:

Chemopreventive effects of 24R,25-dihydroxyvitaminD3 on glandular stomach carcinogenesis induced in rats by N-methyl-N'-nitro-N-nitrosoguanidine and sodium chloride.

Shinichiro Ikezaki, Akiyoshi Nishikawa, Fumio Furukawa, et al.

Cancer Res 1996;56:2767-2770.

<http://cancerres.aacrjournals.org/content/56/12/2767.full.pdf>
(<http://cancerres.aacrjournals.org/content/56/12/2767.full.pdf>)

24R,25-dihydroxyvitamin D3: an essential vitamin D3 metabolite for both normal bone integrity and healing of tibial fracture in chicks.

Seo EG, Einhorn TA, Norman AW

Endocrinology. 1997 Sep;138(9):3864-72.

<http://www.ncbi.nlm.nih.gov/pubmed/9275076> (<http://www.ncbi.nlm.nih.gov/pubmed/9275076>)

and from the same authors:

Studies on 24R,25-dihydroxyvitamin D3: evidence for a nonnuclear membrane receptor in the chick tibial fracture-healing callus.

Kato A, Seo EG, Einhorn TA, Bishop JE, Norman AW.

Bone. 1998 Aug;23(2):141-6.

<http://www.ncbi.nlm.nih.gov/pubmed/9701473> (<http://www.ncbi.nlm.nih.gov>

/pubmed/9701473)

Also:

The serum 24,25-dihydroxyvitamin D concentration, a marker of vitamin D catabolism, is reduced in chronic kidney disease.
Bosworth CR, Levin G, Robinson-Cohen C, Hoofnagle AN, Ruzinski J, Young B, Schwartz SM, Himmelfarb J, Kestenbaum B, de Boer IH.
Kidney Int. 2012 Sep;82(6):693-700. doi: 10.1038/ki.2012.193. Epub 2012 May 30.
<http://www.ncbi.nlm.nih.gov/pubmed/22648296> (<http://www.ncbi.nlm.nih.gov/pubmed/22648296>)



Tom Weishaar says:

October 26, 2013 at 6:42 am (<https://www.vitamindcouncil.org/blog/three-versions-of-vitamin-d-can-activate-the-vitamin-d-receptor-in-some-cells/#comment-3346>)

Ian – thanks for all the links. This makes it clear why the researchers included 24,25-D in their study.



Tom Weishaar says:

October 26, 2013 at 6:47 am (<https://www.vitamindcouncil.org/blog/three-versions-of-vitamin-d-can-activate-the-vitamin-d-receptor-in-some-cells/#comment-3347>)

I forgot to mention that in this study the three forms of vitamin D were all the D3 (animal) forms. It would be interesting to find out if the D2 (plant) forms activate the same genes, as well as whether substances that seem to mimic some of the metabolic effects of vitamin D, such as curcumin (found in turmeric), activate anything,



Rita and Misty says:

October 26, 2013 at 4:56 pm (<https://www.vitamindcouncil.org/blog/three-versions-of-vitamin-d-can-activate-the-vitamin-d-receptor-in-some-cells/#comment-3348>)

Inflammation is the culprit of modern day disease(s)...in my opinion we need to look back to Africa...to our ancestral origins...for healthy inspiration:

- * appropriate sun exposure for optimal 25(OH)D level
- * paleo/primordial eating habits to improve gut health
- * adequate exercise and sleep
- * establishment of social networks

These all play a role in our good health.



Ian says:

October 27, 2013 at 2:10 pm (<https://www.vitamindcouncil.org/blog/three-versions-of-vitamin-d-can-activate-the-vitamin-d-receptor-in-some-cells/#comment-3350>)

Tom I would also like to see some information on the D2 analogue in the catabolism to 24,25(OH)2D. I suspect the kinetics of the conversion are different. Kinetics do play an important part in function and availability, I suspect particularly in epigenetic function, something many researchers forget to study or include in analyses.

So far much of the comparison of D2 and D3 have been in the comparative levels of 25(OH)D and while equivocal I think more recent studies are saying that D3 supplementation leads to higher 25(OH)D levels.

Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis.
Tripkovic L, Lambert H, Hart K, Smith CP, Bucca G, Penson S, Chope G, Hyppönen

E, Berry J, Vieth R, Lanham-New S.
Am J Clin Nutr. 2012 Jun;95(6):1357-64. doi: 10.3945/ajcn.111.031070. Epub 2012 May 2.

Long-term vitamin D3 supplementation is more effective than vitamin D2 in maintaining serum 25-hydroxyvitamin D status over the winter months.
Logan VF, Gray AR, Peddie MC, Harper MJ, Houghton LA.
Br J Nutr. 2013 Mar 28;109(6):1082-8. doi: 10.1017/S0007114512002851. Epub 2012 Jul 11.

ABOUT THE VITAMIN D COUNCIL

The Vitamin D Council is a 501(c)(3) nonprofit organization, working to educate the public on vitamin D, sun exposure and health.

See our About us (/about-us/) page for more information.

CONTACT US

Vitamin D Council
1241 Johnson Ave. #134,
San Luis Obispo, CA 93401
United States

1-805-439-1075
info@vitamindcouncil.org
(mailto:info@vitamindcouncil.org)

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