A multidisciplinary review of the science of vitamin D receptor activation

Kidney International Supplements (2011) **1**, 107–110. doi:10.1038/kisup.2011.25

KEYWORDS: cardio-renal syndrome; chronic kidney disease; CKD–MBD; vascular calcification; VDR; VDR activation; vitamin D

Mario Cozzolino[1], Jordi Bover[2], Marc Vervloet[3] and Vincent M. Brandenburg[4]
[1]Department of Medicine, Surgery, and Dentistry, Renal Division, S. Paolo Hospital, University of Milan, Italy, [2]Nephrology Department, Fundació Puigvert, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Catalonia, Spain, [3]Department of Nephrology, VU University Medical Center, Amsterdam, The Netherlands and [4]Department of Cardiology, University Hospital Aachen, Aachen, Germany.
Correspondence: *Mario Cozzolino, DMCO, Renal Division, S. Paolo Hospital, University of Milan, Via A. di Rudinì, 8 – 20142 – Milan, Italy. E-mail: mario.cozzolino@unimi.it*

AIMS AND SCOPE OF THE VDR EXPERT CENTERS INITIATIVE

Our understanding of the vitamin D receptor (VDR) and the effects of VDR activation has changed dramatically in recent years, with the publication of several new studies looking at selective VDR activation and effects on the cardio-renal syndrome (CRS).[1] These advances have the potential to change the perspective of VDR activation beyond its role in mineral metabolism. Pleiotropic vitamin D effects have come into the focus of interest. The VDR Expert Centers are an independent scientific organization comprising a group of European academic medical centers aligned to enhance the scientific understanding of the VDR. The group is focused on increasing research collaborations, medical education, and the dissemination of knowledge in the field of VDR activation. A fellows' educational program runs alongside and is intended to increase interest and build skills in clinicians and researchers entering the field. Additionally, the VDR Expert Centers collaborate on research and other projects concerned with the VDR, including an annual Grand Rounds symposium, which brings together experts in the field to share the latest information in this area. This supplement serves as a review of the data that were discussed at the inaugural Grand Rounds symposium in Amsterdam in September 2010.

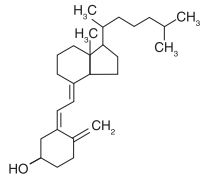
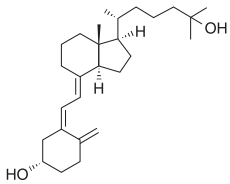
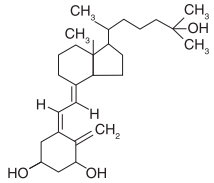
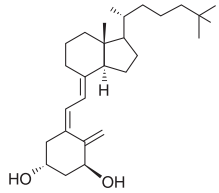
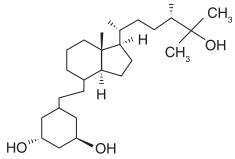
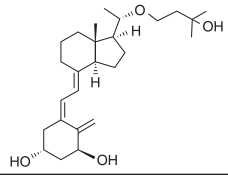
A CALL FOR HOMOGENOUS NOMENCLATURE

Alongside the scientific advancements surrounding the VDR, at both preclinical and clinical levels, it is clear that the nomenclature for vitamin D and VDR activators has become more complex, though not necessarily consistent. Here, the authors of this supplement have agreed to standardize terms between the articles, so that it is clear from the outset to what molecule each author refers. For clarity in interpreting the results of each investigation, compounds are distinguished precisely; they have different structures, some are inactive, some activate the VDR, and not all are detectable in the assays performed to obtain a 'vitamin D' level in our patients. Table 1 provides a summary of the vitamin D and VDR activator nomenclature used in the articles in this supplement, the final column to the right containing the preferred shorthand term used here. Throughout, this allows for a comparison of each study and a recognition that each compound may act differently on the same receptor.

FIGHTING VITAMIN D DEFICIENCY: WHAT ARE APPROPRIATE VITAMIN D LEVELS?

Another important issue regarding consistency in the field of vitamin D is the recommended target level of 25-hydroxyvitamin D (25D), both in the general population and in chronic kidney disease (CKD) patients. The debate continues about how much 25D is enough or too much. There is a lack of agreement between various guidelines and experts in what clinical levels of 25D are required and also how much has to be taken as supplements to achieve this. Recommendations and guidelines for optimum vitamin D levels are currently based on epidemiological and observational data and randomized controlled trials related to vitamin D intake and health outcomes are few. Vitamin D deficiency in the general population with normal renal function causes secondary hyperparathyroidism (SHPT), bone loss, and is strongly associated with a higher risk for hypertension, proteinuria, cardiovascular (CV) lesions, and higher rates of CV mortality.[2] This exemplifies the broad role that vitamin D has in several biological processes for the maintenance of general health. Nevertheless, various professional groups currently recommend different levels of 25D for optimal efficacy. For example, pulmonologists interested in cystic fibrosis, a condition where vitamin D deficiency is common, recommended maintaining 25D levels above 35 ng/ml (87.5 nmol/l) for individuals with cystic fibrosis to avoid SHPT and bone loss.[3] The Institute of Medicine of the National Academies (IOM)

Table 1. Vitamin D and VDR activator nomenclature

Class of compounds	Description	Name	Molecule	Structure	Standardized nomenclature
Vitamin D	Dietary or native vitamin D	Cholecalciferol Ergocalciferol	Vitamin D_3 Vitamin D_2		Native vitamin D
	Product of the first hydroxylation of vitamin D in the liver	Calcidiol	25-hydroxyvitamin D		25D
Active vitamin D	Product of the second hydroxylation of vitamin D in the kidneys. Binds the VDR directly	Calcitriol	1,25-dihydroxyvitamin D_3		1,25D
	A synthetic analog of calcitriol, converted to calcitriol in the liver before binding the VDR	Alfacalcidol	1α-hydroxyvitamin D_3		1-alpha
Selective VDR activator	Acts as a synthetic agonist to the VDR, but is not converted to calcitriol before binding. Selectively activates downstream pathways (i.e., less effect on Ca and P absorption in the gut)	Paricalcitol	19-NOR-1α dihydroxyvitamin D_2		Selective VDR activator
		Maxacalcitol	22-oxa-1,25-dihydroxyvitamin D_3		Selective VDR activator

recently published guidelines on vitamin D supplementation for the general population, which were much lower.[4] The IOM stated that, based on available data, almost all individuals have sufficient 25D when their blood levels are >20 ng/ml (50 nmol/l) and that there is little additional benefit above 30 ng/ml (75 nmol/l). In these guidelines, bone health was selected as the indicator to serve as the basis of the Dietary Reference Intake (DRIs) for Ca and vitamin D. They found compelling evidence supporting the role for Ca and vitamin D in skeletal health. On the other hand, the report was inconclusive as to whether supplementing with native vitamin D or Ca is of benefit in non-skeletal outcomes. These non-skeletal outcomes are exactly what make us question whether the recent IOM recommendations are justified. Limiting the appropriate vitamin D level to 20 ng/ml of 25D has initiated a vigorous scientific debate in the international literature. Currently, the VDR Expert Centers group, in line with the previous 2003 K/DOQI guidelines[5] and the recent Spanish recommendations for CKD–mineral and bone disorder (CKD–MBD) have decided to suggest a 25D target level of >30 ng/ml.[6] Consequently, this VDR Expert Centers group essentially agrees that 25D levels of

20 ng/ml are too low for the well-being of CKD patients, and that levels of >30 ng/ml would maximize benefit.

The debate on optimum 25D levels are discussed in detail by the authors in this supplement. In their article, Pilz *et al.* reflect that most CKD patients are 25D deficient, with levels below the target of 30 ng/ml; the authors discuss the subsequent negative consequences for an increased risk of CV diseases and CV mortality. Hence, their group recommend testing for 25D levels and treating deficiency, according to current KDIGO guidelines, and aim, in general, for a sufficient vitamin D status with 25D levels of $\geqslant$30 ng/ml, the ideal target level according to many sources.[5–9]

VITAMIN D: WHEN IS ENOUGH TOO MUCH?

However, Adriana Dusso discusses all the plausible advantages and problems of further increasing vitamin D levels, acknowledging that levels of 25D above 50 ng/ml may be detrimental to health and survival.[10] In any case, increases in plasma Ca and/or P, and probably increases in calciuria, may represent indirect evidence of undesirable high levels of 25D. Cozzolino and Bover address the issues of vitamin D levels and effect on mineral metabolism and bone, as well as their relation to the vasculature. The authors agree that the evidence points to a narrow range of 25D levels at which vascular function is optimized.[11] The VDR Expert Centers group acknowledges the fact that vitamin D is a potent hormone for which the risk of potential side effects correlates with high storage levels. However, we feel that any upper level of recommendation is even less well defined than the lower 25D level of >30 ng/ml. Exploring the optimal range of vitamin D levels in CKD patients, avoiding undertreatment as well as oversupplementation, is one of the main future research topics of the VDR Expert Centers group.

VITAMIN D AND CLOSELY RELATED ISSUES OF CKD–MBD

The review by Brandenburg *et al*. highlights the substantial developments that have taken place in the VDR arena in the past decade. Specifically, actions of the VDR in the heart have been explored, and the importance of vascular calcifications in CKD as the cause of significant morbidity and mortality has been documented. The authors have selected what they believe are landmark publications that have improved our understanding of the mechanisms involved in the development of what they term 'vascular calcifications in uremia,' as well as the clinical approaches we now have to improve vascular health in CKD. They touch on an article that introduced Klotho and FGF23 into the world of nephrology, and in their review Vervloet and Larsson explore in depth the fascinating discovery and mechanisms of action of these compounds. Importantly, FGF23 is a potent negative regulator of circulating P and 1,25D, so it will be interesting to see how its clinical implications in CKD as a biomarker and/or therapeutic target develop.

PERSPECTIVES

Looking to the future, randomized, controlled trials for optimizing the treatment of CKD–MBD are still needed, and more work is required to define optimal target levels of Ca, P, PTH and vitamin D—as well as the new players, FGF23 and Klotho—in this population. There is also the need to define the potential differences between VDR activation with the administration of native, active, or selective forms of VDR activators. What is clear from all the articles in this supplement is that lack of VDR activation in CKD patients is a significant problem that is associated with accelerated renal and CV disease progression and death.[12,13] The safe correction of this deficiency without disturbing the Ca and P balance is becoming a high priority for nephrologists.

DISCLOSURE

This issue was organized by the VDR Expert Centers and was funded by Abbott Laboratories with a collaborative effort to advance and support the science and the improvement of quality of life for renal patients.

CONTRIBUTORS

MC has given national and international lectures with the sponsorship of Abbott, Amgen, Genzyme, Shire, and Roche. JB is part of the Spanish advisory boards for Abbott and Amgen, and he collaborated in advisory boards for Genzyme. JB has given national and international lectures with the sponsorship of Abbott, Amgen, Genzyme, and Shire. MV has received consulting fees from and/or participated in paid advisory boards for Amgen, Abbott Laboratories, and Fresenius; received lecture fees from speaking at the invitation of Abbott Laboratories and Amgen; and received grant support from Genzyme and Shire. VMB has received consulting fees from and/or participated in paid advisory boards for Genzyme, Abbott Laboratories, and Amgen; received lecture fees from speaking at the invitation of Fresenius, Shire, Genzyme, Amgen, Novartis, and Abbott Laboratories; and received grant support from Amgen, Genzyme, and Fresenius.

REFERENCES

1. Ronco C, Cozzolino M. Mineral metabolism abnormalities and vitamin D receptor activation in cardiorenal syndromes. *Heart Fail Rev*; e-pub ahead of print 13 February 2011.

2. Adams JS, Hewison M. Update in vitamin D. *J Clin Endocrinol Metab* 2010; **95**: 471–478.
3. West NE, Lechtzin N, Merlo CA *et al*. Appropriate goal level for 25-hydroxyvitamin D in cystic fibrosis. *Chest*; e-pub ahead of print 10 March 2011.
4. Institute of Medicine. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: The National Academies Press; 2011, p 1015. Full Report: http://books.nap.edu/openbook.php?record_id=13050. Brief Report: http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D/Report-Brief.aspx.
5. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003; **42**(4 Suppl 3): S1–S201.
6. Torregrosa JV, Bover J, Cannata Andía J *et al.* Spanish Society of Nephrology recommendations for controlling mineral and bone disorder in chronic kidney disease patients (SEN-MBD) *Nefrologia* 2011; **31**(Suppl 1): 3–32.
7. Souberbielle JC, Body JJ, Lappe JM *et al*. Vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: recommendations for clinical practice. *Autoimmun Rev* 2010; **9**: 709–715.
8. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007; **357**: 266–281.
9. Kidney-Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int Suppl* 2009; **113**: S1–S130.
10. Melamed ML, Michos ED, Post W *et al*. 25-hydroxyvitamin D levels and the risk of mortality in the general population. *Arch Intern Med* 2008; **168**: 1629–1637.
11. Hsu JJ, Tintut Y, Demer LL. Vitamin D and osteogenic differentiation in the artery wall. *Clin J Am Soc Nephrol* 2008; **3**: 1542–1547.
12. Melamed ML, Astor B, Michos ED *et al*. 25-hydroxyvitamin D levels, race, and the progression of kidney disease. *J Am Soc Nephrol* 2009; **20**: 2631–2639.
13. Cozzolino M, Ketteler M, Zehnder D. The vitamin D system: a crosstalk between the heart and kidney. *Eur J Heart Fail* 2010; **12**: 1031–1041.