

Why “Vitamin D” is not a hormone, and not a synonym for 1,25-dihydroxy-vitamin D, its analogs or deltanoids[☆]

Reinhold Vieth*

Department of Laboratory Medicine and Pathobiology, University of Toronto and Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, Ont., Canada M5G 1X5

Abstract

Official nutrition committee reports in both North America and Europe now state that Vitamin D is more of a hormone than a nutrient. These statements are wrong, and do not reflect the definitions of either vitamin or hormone. Researchers often compound the problem by referring to calcitriol or other deltanoids as “Vitamin D”. These things have serious consequences: (1) The literature is burdened by an ongoing confusion that presumes that the reader will somehow “know” what the writer refers to by “Vitamin D”. (2) Medical practitioners not familiar with the ambiguities administer Vitamin D inappropriately when calcitriol or a deltanoid analog would be correct, or vice versa. (3) Attempts to promote Vitamin D nutrition are hindered by alarmist responses justifiably associated with the widespread administration of any hormone. Vitamin D is a vitamin in the truest sense of the word, because “insufficient amounts in the diet may cause deficiency diseases”. The term, prohormone, is not relevant to the Vitamin D system, but 25-hydroxy-Vitamin D (calcidiol) is appropriately described as a prehormone, i.e. a glandular secretory product, having little or no inherent biologic potency, that is converted peripherally to an active hormone.

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1. Introduction

There is probably no other area of steroid biochemistry so burdened by terminological complexity as the field of Vitamin D. In several ways, Vitamin D falls between the cracks of definitions applied to it. First, there is confusion about whether Vitamin D is truly a vitamin or nutrient, and that perhaps the word, hormone, is more suitable. Second, the “Vitamin D” is used in the generic sense far too often, to substitute for 1,25-dihydroxyvitamin D (calcitriol) or for any molecule based upon Vitamin D’s secosteroid structure.

Some consequences of the widespread erroneous use of terminology in the field of Vitamin D are as follows:

- (i) The literature suffers from an ongoing confusion created by writers who assume that readers will somehow “know” what is being referred to by the term, “Vitamin D”. Any quick search of the contemporary literature will show that it is common, even for experienced specialists, to have difficulty in knowing what compounds that articles dealing with “Vita-

- min D” are about. The PubMed research website, (<http://www4.ncbi.nlm.nih.gov/PubMed/>), consistently produces articles where the molecule based on Vitamin D (deltanoid) relevant to the article is not discernable from the title, such as the examples cited here [1,2], the abstract [3], and sometimes not even evident from the original article itself [4]. Ambiguities about “Vitamin D” make publications lose credibility and scientific value. Furthermore, free access by the general public to PubMed means that our research abstracts are probably read more often by non-specialists than by the scientific community that was our primary readership in the past. Therefore, we have a responsibility to take greater care in writing those parts of publications that will be widely accessible to the public.
- (ii) Medical practitioners not familiar with the ambiguities surrounding the terminology in the field sometimes administer Vitamin D inappropriately when calcitriol or an analog would be correct, or vice versa (anyone who specializes clinically in the field of Vitamin D knows of examples of such unintended misuse). It is not unusual that Vitamin companies and the public or clinicians sometimes think Vitamin D3 is an abbreviation for calcitriol, or that Vitamin D2 is calcidiol (the source of this confusion should be obvious). A

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* Tel.: +1-416-586-5920; fax: +1-416-586-8628.

E-mail address: rvieth@mtsinai.on.ca (R. Vieth).

Table 1
Definitions pertinent to the Vitamin D system^a

Terms	Definition
Vitamin	One of a group of organic substances, present in minute amounts in natural foodstuffs, that are essential to normal metabolism, insufficient amounts in the diet may cause deficiency diseases. [L. vita, life, + amine]
Hormone	A chemical substance, formed in one organ or part of the body and carried in the blood to another organ or part; depending on the specificity of their effects, hormones can alter the functional activity, and sometimes the structure, of just one organ or tissue or various numbers of them. [G. hormon, pres. part. of hormao, to rouse or set in motion]
Prohormone	An intraglandular precursor of a hormone. eg. <i>pro-PTH</i> , <i>pro-insulin</i> , <i>pro-opiocortin</i>
Prehormone	A glandular secretory product, having little or no inherent biologic potency, that is converted peripherally to an active hormone. eg. <i>dehydroepiandrosterone</i> , <i>T4</i>

^a Definitions of the terms are taken from [11]. Note that the characteristics of calcidiol match the definition of prehormone, and calcitriol matches the definition of hormone. Vitamin D is indeed a vitamin because “insufficient amounts in the diet may cause deficiency diseases”.

dangerous consequence is that in some countries where nutritional Vitamin D is not available in meaningful doses, calcitriol or its analogs are promoted as superior alternatives for treatment or prevention of disease. It is notable that the most thorough overview of Vitamin D, calcitriol and its analogs for osteoporosis treatment and prevention has concluded that there is no evidence that Vitamin D3 (cholecalciferol) is any less effective than calcitriol or its analogs [5].

- (iii) Attempts to promote Vitamin D nutrition are hindered by alarmist responses that are justifiably associated with the widespread administration of any hormone. Consumption of a hormone can imply that homeostatic control is circumvented by an unnatural treatment. To illustrate this, a recent paper in the well-respected, *Journal of the American Geriatric Society*, states, “The best evidence for *hormonal* replacement is Vitamin D and estrogen replacement to prevent hip fractures” [6]. The association of Vitamin D nutrition with hormone-replacement therapy (HRT) now has a bad connotation for otherwise healthy people, because HRT has been shown to increase risk of breast cancer and cardiovascular events [7]. The misconception that Vitamin D is a hormone creates a situation where people who may benefit from Vitamin D will avoid it along with what many regard as the unnecessary use of hormones.

2. Vitamin D is not a hormone

Anyone sincerely interested in nutrition should be concerned that officially mandated nutritional committee reports for both North America and Europe now state that “Vitamin D is a hormone” [8], or that “Vitamin D is more like a hormone” than a vitamin [9]. This reflects confusion that has arisen because some medical dictionaries define a vitamin as an organic micronutrient that must only be present in the diet, this is a feature that certainly does not reflect the true meaning of the term, vitamin, as coined by Funk [10]. The only requirement of a true vitamin is that it is an organic micro-nutrient whose lack in the diet may result in deficiency disease [10,11]. Vitamin D is not alone as a vita-

min attainable by other than dietary means, since niacin can also be synthesized, and vitamin A can be generated in the body from beta-carotene.

By itself, a perceived inadequacy of the term, vitamin, could never have created a default situation where a molecule would come to be regarded as a hormone. However, the realization that the kidney functions as a classic endocrine gland, to produce the calcium-regulating hormone, calcitriol, opened the door for some to start referring to Vitamin D as a hormone. Adherents of the Vitamin D is a hormone concept never offer a full explanation of the logic for it. One fallback position for adherents is to state, “Vitamin D is a prohormone”. This is also not valid. A prohormone refers to a committed intra-glandular precursor of a hormone. The most notable examples of pro-hormones are pro-PTH and pro-insulin.

For most of the 20th century, there was no debate that Vitamin D was a nutrient. It was “the sunshine vitamin”, and I contend that we should maintain that perspective. A focus on a poor definition of the word, vitamin, in some dictionaries is no excuse to allow the misconception to continue, that Vitamin D might be regarded as a hormone instead of a nutrient. For reference, more rigorous definitions of words pertinent to vitamin and hormone are presented in Table 1. It should be evident from this that Vitamin D is no more a hormone than cholesterol is—both are the structural raw material that one or more hormones are made from. Vitamin D is a vitamin in the truest sense of the word, because “insufficient amounts in the diet may cause deficiency diseases”.

3. Calcitriol or 1,25(OH)₂D is not Vitamin D

The attribution that a substance was a vitamin was never based upon molecular structure. Early in the last century, vitamins were identified and defined based on their bioactivity [10]. “Vitamin D” was any preparation that did what Vitamin D was thought to do i.e. to facilitate bone mineralization. This activity was measured in International Units that were determined by the rat-line test last done more than 50 years ago. In 1981, when the International Union of Pure and Applied Chemistry and International Union

of Biochemistry and Molecular Biology Joint Commission on Biochemical Nomenclature (IUPAC) established Nomenclature of Vitamin D, its approach to terminology was a holdover from the concept that a vitamin is defined by its bioactivity. IUPAC referred to “Vitamin D” as a class of “steroids that exhibit qualitatively the biological activity of calcitriol” (cholecalciferol) [12]. After 20 years, that definition has surely become outdated. How can we continue to justify use of a bioactivity-based definition for this class of steroids, when all of the “Vitamin D analogs” that have been developed for clinical use exist for the very purpose of *not* exhibiting the full spectrum of Vitamin D’s bioactivity?

Just as the word “steroid” encompasses the hormones and drugs derived from the cholesterol molecule, the term, “secosteroid”, or a suggested alternative, “deltanoids” [13], would be the equivalent generic term for the compounds derived from the cholecalciferol molecule. As a research community, we need to develop a consensus on the appropriate terminology, and the generic term must not be, “Vitamin D”.

Regrettably, the way many authors have dealt with the problems surrounding the terminology of Vitamin D has been to resort to use of the most general term that IUPAC allows for compounds in this class, and they refer to everything in the field as “Vitamin D”. This approach makes this already complex field worse by adding ambiguity. Sometimes there are attempts at being specific, by referring to “plain Vitamin D” [14], or “the Vitamin D hormone”. But since official nutrition guidelines now state (incorrectly) that cholecalciferol is a hormone [8,9] such attempts at clarification are feeble, and no longer helpful to many readers.

Fortunately, IUPAC did provide simple, useful terminology, offering cholecalciferol, calcidiol, and calcitriol for Vitamin D and its most clinically relevant metabolites. IUPAC frowned on written usages of the style, 25(OH)D and 1,25(OH)2D, but these remain unambiguous, and they continue to be in wider use than either calcidiol or calcitriol. Both approaches to the terminology (i.e. the formats of calcitriol or 1,25(OH)2D) are clear, and they will not confuse anyone.

Before 1970, use of the term “Vitamin D” referred only to either ergocalciferol or cholecalciferol; Vitamin D2 or Vitamin D3, respectively. These words continue to express what the public, including authors of peer-reviewed articles, should be expecting to get when they purchase Vitamin D in the pharmacy. Therefore, it does not make sense that those same authors use the term, Vitamin D, as a substitute for any number of other compounds when they publish research findings. Some might argue that use of the word “Vitamin D” in the title is a simple and useful way to ensure that others will find the publication easily, or that the nutritional implication of the word adds dramatic impact to papers that actually deal with other deltanoids. A recent paper by Matheu et al. [3] is worth reading as a classic

example of the misuse of nutrition terminology to frame what was in reality a pharmacologic study having nothing to do with nutrition. By now, the message should be clear, that the practice of substituting the word “Vitamin D” for any deltanoid creates more confusion than clarity. The objective of a PubMed search term is achieved just as well by including “Vitamin D” among key words, instead of in the title.

The onus for dealing with the problem of Vitamin D terminology lies in the hands of the Vitamin D research community. As authors and as reviewers, part of the job of good science is to guide editors of journals to a higher standard concerning our field of interest. There is no dignity in allowing poor communication to go unchallenged.

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