

Vitamin D: Are we Ready for a New Era? Revisiting the Concept of Vitamin D Sufficiency Beyond Skeletal Health

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Abstract

In a previous paper, we addressed several important issues concerning the actual physiological behavior of vitamin D (Vit D), focusing not only on its metabolism but, more importantly, on its biological effects in the numerous extrarenal cells capable of expressing either the Vit D receptor (VDR) or the enzyme CYP27B1. We also highlighted several unresolved questions regarding the relative contribution of renal calcitriol production compared with that generated within extrarenal tissues, as well as the molecular mechanisms regulating CYP27B1 expression. Despite the considerable advances in our understanding of calcitriol biology, many questions still require further clarification.

Among these, particular attention should be paid to the mechanisms regulating the entry of 25-hydroxyvitamin D (25OHD) into extrarenal cells, its subsequent intracellular fate, the optimal concentrations required for biological activity, and the mechanisms underlying its depletion.

Keywords: Vitamin D Metabolism; Vitamin D Receptor; CYP27B1 Expression; Extrarenal Tissues; DBP; Megalin-Cubilin

Introduction

It is well established that 25-hydroxyvitamin D (25OHD, calcidiol) is a lipophilic molecule. In the circulation, it is bound predominantly to Vit D-binding protein (DBP) and, to a lesser extent, to albumin. Only a very small fraction remains unbound and is therefore available to enter cells through several mechanisms [1].

One of the principal pathways appears to be passive diffusion of the free fraction. Owing to its lipophilic nature, a small amount of free 25OHD can cross the plasma membrane without the need for specific transport systems [2].

In addition, some tissues express megalin- and cubilin-mediated endocytic systems that facilitate the uptake of the DBP-25OHD complex. However, the quantitative contribution of these mechanisms outside the kidney remains incompletely defined and appears to depend on both cell type and physiological context [3].

It is reasonable to assume that not all cells within a given tissue continuously require 25OHD for metabolic purposes. Rather, cellular demand is likely influenced by transient physiological or pathological conditions that increase local Vit D utilization. If a cell does not express CYP27B1, or expresses it only at very low levels, intracellular 25OHD is not significantly converted into calcitriol. In other words, substrate availability alone is insufficient; activation of the enzymatic machinery is also required.

Many tissues—including immune cells, skin, prostate, breast, colon, placenta, and others—can upregulate CYP27B1 expression in response to local signals such as inflammatory cytokines, growth factors, and immune mediators. Under these conditions, cells increase the conversion of available 25OHD into calcitriol according to both enzyme abundance and cellular requirements [4].

The remaining intracellular 25OHD may subsequently be converted into calcitriol, remain temporarily available within the cell, or undergo catabolism by CYP24A1, the enzyme responsible for degrading both calcitriol and excess 25OHD. Thus, an autoregulatory mechanism exists that tightly controls intracellular calcitriol concentrations. When calcitriol levels become excessive, CYP24A1 expression may be induced, CYP27B1 expression reduced, and additional negative feedback pathways activated. As a consequence, further calcitriol synthesis is suppressed and excess hormone is degraded.

A fundamental concept is that the concentration of free 25OHD in plasma is extremely low and is continuously replenished by the large circulating reservoir represented by DBP-bound 25OHD [5]. Consequently, under normal physiological conditions, there is no competition among tissues leading to depletion of systemic Vit D stores. In many physiological settings, the principal limiting factor appears to be the balance between enzymatic activation and inactivation of Vit D metabolites, although the relative contribution of transport mechanisms and free 25OHD availability may vary among different tissues.

New questions

We have acquired extensive knowledge regarding the biochemistry of Vit D, including the enzymes, receptors, and feedback circuits that regulate its metabolism. However, when moving from the molecular level to the level of the whole organism, many important questions remain unanswered:

- What is the actual physiological relevance of free versus protein-bound 25OHD?
- How does Vit D metabolism and action vary among different tissues?
- What is the relative contribution of locally produced calcitriol compared with renal calcitriol production?
- Which mechanisms precisely regulate intracellular 25OHD availability?
- To what extent do factors that remain poorly understood, such as the cellular microenvironment and intracellular compartmentalization, influence Vit D activity?

These questions prompt a critical reappraisal of traditional concepts of Vit D sufficiency and insufficiency.

The conventional definition of Vit D sufficiency (serum 25OHD ≥ 20 ng/mL according to many guidelines, or ≥ 30 ng/mL according to others) is derived almost exclusively from its effects on calcium-phosphate metabolism and skeletal health. However, if Vit D is viewed as a much broader endocrine-paracrine system, the issue becomes considerably more complex.

Many extrarenal cells including macrophages, dendritic cells, T and B lymphocytes, intestinal epithelial cells, prostate cells, mammary epithelial cells, endothelial cells, and others—express both the vitamin D receptor (VDR) and the enzyme 1 α -hydroxylase (CYP27B1). These cells are therefore capable of converting circulating 25OHD into calcitriol locally in order to regulate tissue-specific gene expression. In these settings, circulating 25OHD serves as the substrate available for intracellular calcitriol synthesis [6].

As a consequence, each cell type may respond differently according to its specific pattern of VDR expression, CYP27B1 activity, and CYP24A1-mediated calcitriol degradation. Furthermore, physiological conditions and local stimuli may alter cellular requirements for Vit D metabolites and consequently modify substrate demand [7].

Therefore, serum 25OHD concentrations do not necessarily reflect, in a proportional manner, intracellular substrate availability within different tissues. Factors such as free 25OHD concentrations, Vit D-binding protein (DBP) levels, and the presence of cellular transport mechanisms including megalin, cubilin, and potentially other transport systems may be of greater importance in determining tissue-specific Vit D availability.

For these reasons, it appears unlikely that a single circulating concentration of 25OHD can be considered optimal for all cell types and under all physiological conditions.

Several theoretical, yet unvalidated, hypotheses have proposed that serum 25OHD concentrations required to optimize extraskeletal functions may be higher than those necessary to maintain skeletal health alone. Experimental and observational studies have suggested that certain immune functions may be supported by 25OHD concentrations above those traditionally regarded as sufficient for bone metabolism. However, there is currently no consensus regarding an optimal threshold applicable to all immune functions or to all individuals.

Moreover, it should be emphasized that the relationship between serum 25OHD concentration and biological response is unlikely to be linear. Individual variability in VDR polymorphisms, DBP characteristics, and the expression of Vit D-metabolizing enzymes may substantially influence tissue responsiveness to a given circulating 25OHD concentration.

Conclusion

Current evidence does not demonstrate that the serum 25OHD concentration considered optimal for skeletal metabolism necessarily corresponds to that required to ensure adequate substrate availability for all autocrine and paracrine functions throughout the body.

A key unresolved scientific question is whether a systemic concentration of 25OHD exists that can provide an adequate substrate supply to all cells and tissues simultaneously. Indeed, it cannot be assumed that the concentration required for optimal skeletal health coincides with that needed to support the diverse autocrine and paracrine activities occurring in different organs and tissues.

It therefore remains uncertain whether a single serum 25OHD concentration can satisfy the biological requirements of all tissue compartments or whether these requirements are inherently tissue-specific and dependent on both physiological and pathological contexts. If the latter is true, the identification of a universal optimal serum 25OHD concentration for all biological functions of Vit D may prove unattainable.

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