

# Overview of Studies on: Diagnosis and Treatment of Vitamin D-Dependent Rickets

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DOI: <https://doi.org/10.5281/zenodo.8204497>

Published Date: 01-August-2023

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**Abstract:** The term "vitamin D-dependent rickets" describes a group of genetic disorders characterized by early-onset rickets due to the inability to maintain adequate active vitamin D levels or the inability to respond adequately with activated vitamin D. Although the term is now recognized as a pathophysiological misnomer, there is clinical relevance to its continued use, as the patient must be "dependent" for life on the use of a specialized vitamin D replacement regimen. This review examines the molecular basis of the three forms of vitamin D-dependent rickets and summarizes current regimens for the management of affected individuals.

**Keywords:** rickets, genetics, Vitamin D, treatment, hypocalcemia.

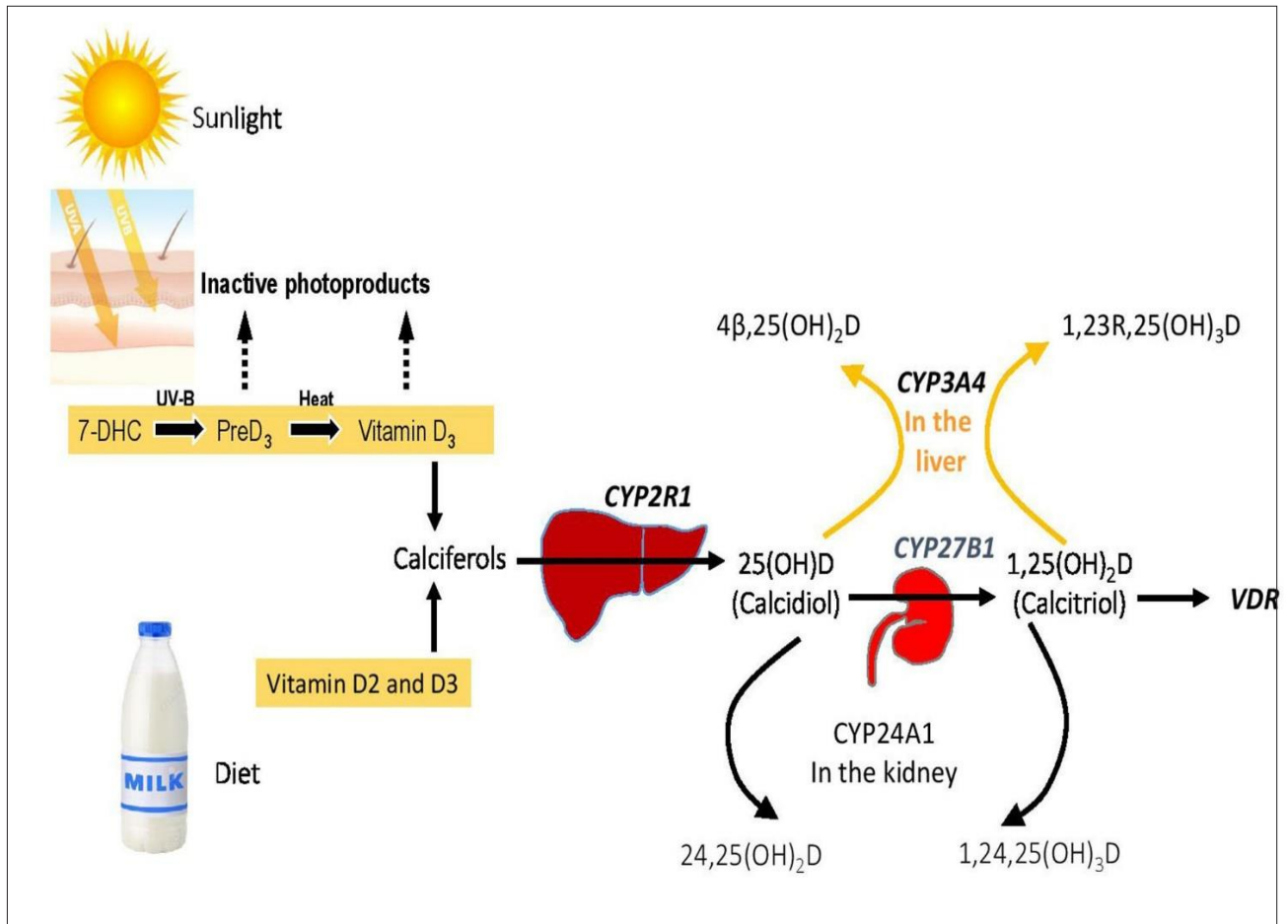
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## 1. INTRODUCTION

The recognition that genetic defects in vitamin D activation or responsiveness could cause rickets evolved from detailed clinical and biochemical studies that identified the critical role that vitamin D played in ensuring normal bone and mineral metabolism. Early studies revealed that rickets was caused by combined nutritional deficiency and a sunless environment, and could be successfully treated with cod liver oil (3). A chemical basis for the therapeutic effectiveness of cod liver oil was first proposed in 1919 by Edward Mellanby (4), and subsequently biochemist Elmer McCollum, working with Johns Hopkins pediatrician John Howland, and later with doctors Edwards A. Alfred Hess and Lester Unger later showed that sunlight was anti-rachitic, an observation that led Harriette Chick to pursue the controlled studies of sunlight and cod liver oil that confirmed the effectiveness of each to prevent rickets. These studies led ultimately to commercial development of vitamin D, providing abundant, inexpensive supplies of vitamin D that enabled widespread prevention and treatment of rickets. The subsequent use of vitamin D (calciferol) for prevention and treatment of rickets and osteomalacia led to marked reductions in their prevalence and clinical burden. Nevertheless, some patients did not respond to the usual doses of calciferols, which led to the recognition of genetic and clinical disorders that impaired activation and/or responsiveness of target tissues to active metabolites of vitamin D. In 1937, Albright reported studies of a child with rickets who failed to respond to the usual doses of vitamin D, and suggested that the basis for the rickets was a hereditary resistance to the actions of calciferols (8). Hereditary cases of rickets that were resistant to calciferols were subsequently recognized, but most patients had biochemical findings that differed from those of nutritional deficiency of calciferol, with normal serum calcium levels. This condition, originally termed familial vitamin D-resistant rickets, was subsequently named X-linked hypophosphatemia (XLH) to acknowledge its X-linked dominant inheritance and the role of primary hypophosphatemia in the development of rickets and osteomalacia.

Today we recognize that there are multiple forms of inherited hypophosphatemic rickets in addition to XLH. True defects in vitamin D responsiveness were first identified as a cause of rickets in 1961, when Prader and colleagues (10) described a distinctive form of hereditary rickets characterized by hypocalcemia and defective bone mineralization, and which did not respond to conventional vitamin D therapy.

This review provides an overview of the growing number of gene defects that interfere with vitamin D action and cause various forms of vitamin D-dependent rickets (VDDR).



**FIGURE 1 | Vitamin D homeostasis and genetic blocks in VDDR. The figure shows the overall metabolic control of vitamin D homeostasis, with the genes involved in various forms of VDDR shown in bold.**

### VITAMIN D HOMEOSTASIS AND RICKETS

Cholecalciferol (vitamin D<sub>3</sub>) is synthesized in a reaction that begins with the opening of the B-ring of 7-dehydrocholesterol to Ergocalciferol (termed vitamin D<sub>2</sub>) is synthesized by opening the B-ring of ergosterol, a sterol present in yeast, fungi, and protozoa. Activation of the parent calciferols cholecalciferol and ergocalciferol requires two hydroxylations. Renal CYP27B1 is tightly regulated, and expression and activity of the enzyme are induced by PTH and suppressed by FGF23.

Vitamin D metabolites 25(OH)D and 1, 25(OH)<sub>2</sub>D may also be modified by the renal cytochrome P450 CYP24A1, which converts these molecules into inactive 24-hydroxylated products.

A secondary pathway for inactivation of vitamin D metabolites is provided by CYP3A4, which is highly expressed in liver and small intestine and which can biotransform a variety of compounds. Genomic actions are mediated by interaction with a high-affinity intracellular nuclear receptor termed the VDR that is analogous to the receptors for other steroid hormones (15), whereas non-genomic actions are mediated by binding of 1,25(OH)<sub>2</sub>D to a presumptive plasma membrane receptor that appears to be identical to classical intranuclear steroid hormone receptors (16).

Ligand- activation of this signaling pathway results in stimulation of MAP-kinase and involves crosstalk with the nuclear VDR [see (17) for review] as well as interaction of membrane receptors with other proteins (e. , ion channels) or signal transduction pathways (e., protein kinase C, cAMP, Ca<sup>++</sup>, etc. Some reports suggest that the membrane-bound vitamin D receptor is important for both fracture healing and chondrocyte maturation (18, 19).

Hypocalcemia, and to some degree calciferol deficiency, results in increased secretion of PTH from the parathyroid glands (i. , secondary hyperparathyroidism), which leads to decreased reabsorption of phosphate and bicarbonate in the proximal renal tubule, resulting in hypophosphatemia and hyperchloremic acidosis, respectively. Reduced serum levels of calcium and/or phosphorus can produce osteomalacia, as the low concentrations of these minerals are insufficient. By contrast, rickets arises as a result of a growth plate defect that in which hypertrophic chondrocytes fail to undergo caspase 9-mediated apoptosis due to reduced concentrations of extracellular phosphate (20).

This effect of hypophosphatemia provides a final common pathway that unifies the growth plate defect of calciopenic forms of rickets (i. , rickets due to deficiency of vitamin D and/or calcium) with that of hypophosphatemic forms of rickets.

The enlarged and disorganized chondrocytes weaken the growth plate and fail to secrete signals that are required for normal replacement of the cartilage template by endochondral bone.

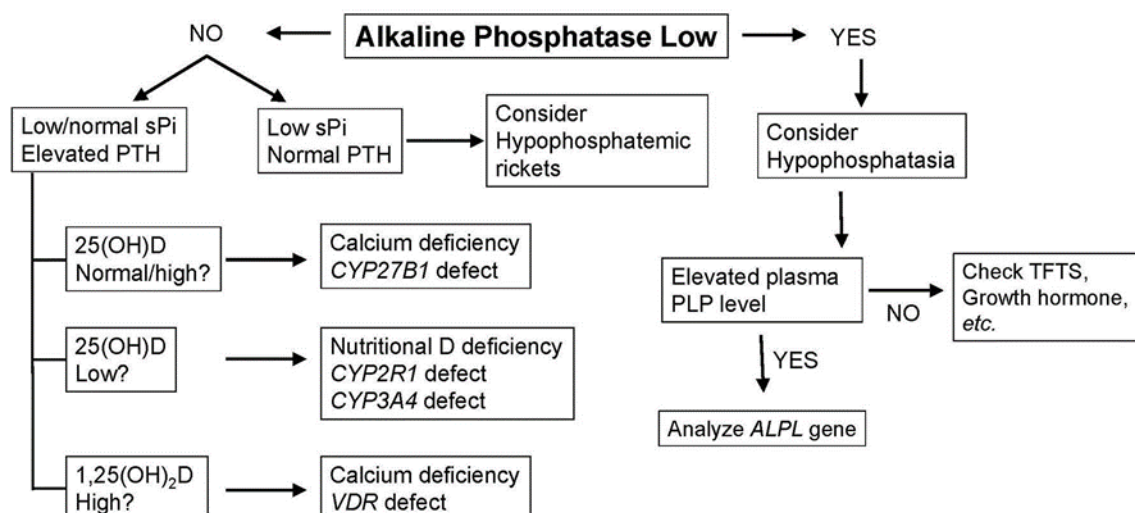
PTH can also act directly on bone to increase osteoclastic reabsorption, but in the absence of adequate 1,2(OH)<sub>2</sub>D action the release of calcium and phosphorus from bone is impaired and cannot fully reverse hypocalcemia or hypophosphatemia.

Because the appearance of the growth plate in children with rickets can resemble that of subjects with hypophosphatasia or metaphyseal dysplasias, a reasonable first step in diagnosis is to determine the serum level of alkaline phosphatase (Figure 2). Using age- and sex-related reference ranges, alkaline phosphatase activity will usually be elevated in rickets, normal in metaphyseal dysplasia, and low in hypophosphatasia.

Subjects who have hypophosphatemia and normal serum levels of PTH, calcium, and 25(OH)D are likely to have phosphopenic rickets; a normal or elevated tubular reabsorption of phosphorus (TRP) will be found in subjects with inadequate intake or absorption of phosphorus.

By contrast, patients with XLH and other genetic or acquired causes of renal phosphate wasting will have reduced TRP values. Subjects with calciopenic rickets will have elevated serum levels of PTH, which depress the TRP and cause.

## Diagnostic Algorithm for Rickets



**FIGURE 2 | A diagnostic algorithm for evaluation of a child with radiological or clinical features of rickets. See text for complete description of biochemical and clinical features of each form of rickets. PLP, Pyridoxal 5'-phosphate, the metabolically active form of vitamin B6; sPi, serum phosphorus; TFTs, thyroid function tests; PLP, pyridoxal 5' phosphate (vitamin B6); ALPL, the gene for tissue non-specific alkaline phosphatase.**

**TABLE 1 | Vitamin D-dependent rickets**

Type	25(OH)D	1,25(OH) <sub>2</sub> D	PTH	Inheritance	Gene defect (OMIM)
VDDR1A	N/I	D	I	A.R.	CYP27B1 (264700)
VDDR1B	D	D	I	A.R.	CYP2R1 (600081)
VDDR2A	N/I	N/I	I	A.R.	VDR (277440)

VDDR, vitamin D-dependent rickets, N, normal; I, increased, D, decreased; PTH, parathyroid hormone.

### VITAMIN D-DEPENDENT RICKETS TYPE 1A (VDDR1A)

Patients with VDDR1a (OMIM 264700) are unable to convert 25(OH)D to 1,25(OH)<sub>2</sub>D owing to biallelic mutations in hypophosphatemia. These subjects have either inadequate intake of calcium and/or vitamin D or genetic defects that impair vitamin D activation or responses (i.e., VDDR). Serum levels of calcium will be normal or decreased based on the severity of the underlying condition.

### VITAMIN D DEPENDENT RICKETS:GENERAL PRINCIPLES

There are three broad categories of VDDR (Figure 1, Table 1). The first is classified as VDDR type 1 (VDDR1), and represents a failure to fully activate calciferols due to the inability to generate either 25(OH)D (VDDR1b) or 1,25(OH)<sub>2</sub>D (VDDR1a). second category is VDDR2, and is characterized by resistance to 1,25(OH)<sub>2</sub>D owing to mutations in the VDR (VDDR2a) or the presence of a nuclear ribonucleoprotein that interferes with the vitamin D receptor-DNA interaction (VDDR2b).

The third category is VDDR3, which results from excessive inactivation of vitamin D metabolites. VDDR shares many clinical and biochemical characteristics with vitamin D deficiency rickets, and Figure 2 provides a suggested diagnostic algorithm.

Table 1 outlines the biochemical features of the various forms of VDDR. Because hypophosphatemia is the unifying basis for all forms of rickets (20), the general principle of VDDR management is to maintain the serum calcium level in the midnormal range to achieve a normal serum level of PTH.

Normalization of the serum PTH concentration will restore normal renal TRP, with consequent correction of hypophosphatemia. Despite this common pathophysiology, the three forms of VDDR show important differences in the biochemical profile of circulating vitamin D metabolites, the therapeutic approach, and in the genetic defect in vitamin D metabolism or action (Figure 2, Table 1).

Patients should be monitored regularly to detect potential asymptomatic hypo- or hypercalcemia, to ensure that growth is normal, to observe changes in the shape or structure of the bones, and to determine whether rickets is active. Serum (calcium, phosphorus, PTH, alkaline phosphatase, creatinine, and appropriate vitamin D metabolites) and urinary (24- h urine calcium or random urine calcium/creatinine ratio) biochemistries should be measured every 3–6 months. Affected subjects appear normal at birth but problems related to impaired vitamin D activity become obvious at 2–24 months. If diagnosed later, fractures, and typical skeletal features of rickets (e. , frontal bossing, long-bone deformities, and rib cage abnormalities) as well as impaired growth are important clinical features.

Biochemical studies show hypocalcemia, hypophosphatemia, and elevated serum levels of alkaline phosphatase and parathyroid hormone.

By contrast, plasma concentrations of 25 (OH)D are normal or increased, likely reflecting the effects of both vitamin D supplementation and decreased clearance of 25 (OH)D due to lack of induction of CYP24A1 by the absence of 1,25(OH)<sub>2</sub>D. With adequate treatment there is healing of rickets and normal growth.

All available calciferol analogs have been successfully used to treat patients with VDDR1a (22–25), but activated forms of vitamin D, such as calcitriol, offer significant advantages: (1) 1,25 (OH)<sub>2</sub>D<sub>3</sub> is the deficient hormone and therefore, physiologic doses of calcitriol are effective; (2) Due to the relatively short half- life of calcitriol, there is a rapid onset of action and unintentional hypercalcemia resolves within days of discontinuation of the drug; and (3) calcitriol is available for oral administration as either a small capsule or a suspension and can also be given intravenously.

Calcitriol is usually administered twice per day owing to its short half-life.

Treatment with  $1\alpha$ -cholecalciferol is similarly effective as this metabolite also overcomes the enzymatic block, and due to its longer half-life than calcitriol, it can be administered once daily.

Because high concentrations of 25(OH)D can bind and activate the VDR, it is also possible to use parent vitamin D (ergocalciferol or cholecalciferol) or 25(OH)- vitamin D (calcifediol), but these analogs must be administered at pharmacologic doses, which carries a greater risk of inducing hypercalcemia.

During successful treatment with vitamin D or calcifediol, serum levels of 25(OH)D levels will be very high (e. , 150–250 ng/mL), but the plasma concentration of 1,25 (OH)2D can remain low or even undetectable (26, 27).

Because of the long half-life of 25(OH)D, these drugs afford once-daily During the first 3–6 months of treatment, patients should be given calciferols in doses 2–5 times those expected for long-term maintenance (Table 2), as the under mineralized skeleton requires unusually large amounts of calcium.

Calcium supplements (50 mg/kg of elemental calcium per day for children) should also be given during initial treatment to prevent worsening of hypocalcemia due to the “hungry bones” phenomenon that occurs with remineralization of the skeleton.

With successful therapy, the fractional absorption of calcium in the intestine remains constant and levels of calcium in the serum (and urine) can fluctuate greatly with variations in the dietary intake of calcium.

**TABLE 2 | Suggested calciferol doses for maintenance treatment of patients with VDDR.**

	VDDR1A	VDDR1B	VDDR2	VDDR3
	( $\mu\text{g}$ per day)	( $\mu\text{g}$ per day)	( $\mu\text{g}$ per day)	( $\mu\text{g}$ per day)
Vitamin D3 or D2	NI	100–200	125–1,000?*	1,000 to?
Calcifediol	NI	20–50	20–200*	50 to?
Calcitriol	0.3–2	0.3–2	5–60 <sup>†</sup>	1 to?
$1\alpha$ (OH)D	0.5–3	0.5–3	5–60 <sup>†</sup>	2 to?

*Dose requirements are uncorrected for body weight and are similar in children and adults. In all cases, supplemental calcium is recommended as described in text. The preferred form of calciferol is noted in bold for each disorder. NI, not indicated.*

*\* Patients with milder grades of resistance to 1,25(OH)2D (usually with normal hair) often can respond to analogs requiring 1-hydroxylation. Maximal useful doses have not been defined. Serum 1,25(OH)2D must be maintained in the range of 200–1,000 pg/mL.*

*†*

*Maximal doses are limited only by cost and patient acceptance; some patients have shown no response to maximal doses tested.*

### **VITAMIN D-DEPENDENT RICKETS TYPE1B (VDDR1B)**

VDDR1b (OMIM #600081) is due to mutations in CYP2R1 that decrease expression or function of the encoded CYP2R1 enzyme, the principal 25-hydroxylase.

VDDR1b is associated with hypocalcemia, secondary hyperparathyroidism and low plasma concentrations of 25(OH)D, with reduced clinical and biochemical responsiveness to conventional doses of vitamin D (28–33). Comprehensive studies in individuals carrying the common p. L99P mutation have provided greater clinical and biochemical insights (30, 32).

Subjects who were homozygous for the p. L99P mutation showed the most severe phenotype, with clinical rickets and very low serum concentrations of 25(OH)D despite extensive sun exposure.

These individuals had undetectable baseline concentrations of 25(OH)D that showed negligible responses to administration of 50,000 IU of cholecalciferol or ergocalciferol (32).

By contrast to other forms of VDDR, which follow a typical autosomal recessive pattern of transmission, relatives who were heterozygous for the p. L99P mutation also showed some evidence of CYP2R1 deficiency, but with less severe childhood bone disease and only modest reductions in circulating concentrations 25(OH)D concentrations.



Remarkably, these abnormalities seemed to improve as the heterozygous subjects Heterozygous patients also show a blunted increase of serum 25(OH)D to administration of 50,000 IU of parent vitamin D (32).

In addition, a second missense mutation, p. K242N, has also been described in a patient from Nigeria (32). Other patients from the Middle East have been reported with compound heterozygous mutations (31).

Several affected individuals from one consanguineous family were homozygous for the p. L99P mutation. The second family contained an affected individual who was homozygous for a novel CYP2R1 mutation, p. G42\_L46delinsR. The clinical phenotype of VDDR1B closely resembles that of VDDR1a, but with a few notable and unique features.

First, the magnitude of vitamin D deficiency and the clinical severity in subjects with CYP2R1 mutations exhibits a gene dosage effect such that the phenotype is milder in patients who carry only one defective allele.

Second, the phenotype appears to improve with age, which may indicate acquisition of a vitamin D- independent mechanism(s) for intestinal absorption of calcium due to development of post-pubertal levels of sex hormones (34).

A common approach is to administer pharmacologic doses of ergocalciferol or cholecalciferol or physiological doses of calcitriol, plus supplemental calcium. showed successful management of one of their patients using alfacalcidol [ $1\alpha$ (OH)D] (33).

The success of this method may depend upon the specific mutation in their patient, who was homozygous for p. G42\_L46delinsR. As for VDDR1a, serum levels of calcium and PTH should be maintained in the mid-normal range, and treatment will be required for life. Patients will require supplemental calcium.

#### **VITAMIN D-DEPENDENT RICKETS TYPE2A (VDDR2A)**

As many patients with this disorder are unable to respond to any form of vitamin D, some have suggested that VDDR2 may be more appropriately described by the terms hereditary 1,25 (OH) $_2$ D- resistant rickets (HVDRR), hereditary resistance to 1,25 (OH) $_2$ D, or even pseudo vitamin D-deficiency, type2A (PDDR IIA).

Patients with VDDR2a appear normal at birth and later develop features of vitamin D deficiency over the first 2–8 months of life. In addition, affected children are born with normal distribution of hair, and alopecia develops later due to failure of normal hair follicle cycling, which is dependent upon unliganded actions of the VDR.

Recent studies have shown that Vdr-null mice develop their initial coat of hair normally, but after the first hair cycle there is impaired reinitiation of anagen (36).

Alopecia appears to be associated with the most severe forms of VDDR2a, based on the very early onset of hypocalcemia and poorest response to therapy. Biochemical studies show low serum levels of calcium and phosphorus and elevated serum concentrations of 1,25(OH) $_2$ D, in the range of 50–1,000 pg/mL (normal in children is 30– 100 pg/mL); serum concentrations of 25(OH)D may be normal or elevated due to lack of induction of CYP24A1, which requires VDR action.

Management during the first few months of life may require only administration of high doses of oral calcium (5–6 g/m $^2$  body surface of elemental calcium).

If oral therapy is able to restore normocalcemia and reverse secondary hyperparathyroidism it may not be necessary to initiate intravenous infusions of calcium.

Nevertheless, successful transition to oral calcium will require substantial doses of calcium salts.

Children with milder forms of VDDR2a, such as those without alopecia, may have clinical and radiologic improvement with administration of high-dose vitamin D therapy that ranges from 5,000 to 40,000 IU per day of calciferol, 20–200  $\mu$ g per day of calcifediol, or 17–20 mcg per day of calcitriol (38).

Many patients will achieve a complete remission if they are receiving very high doses of calciferols (39). with alopecia, about half will be resistant to even the highest doses of calciferols; the other half have demonstrated satisfactory calcemic responses but have required doses that are typically 10-times greater than in those with normal hair.

Some patients will be unable to produce sufficient 1,25(OH)<sub>2</sub>D to overcome the VDR defect but nevertheless will respond to extraordinarily high doses of active forms of vitamin D [i., 1,25 (OH)<sub>2</sub>D<sub>3</sub> or 1 $\alpha$ (OH)D<sub>3</sub>].

Those patients who fail to respond to maximal doses of calciferol will require intravenous infusions of calcium (1,000 mg elemental calcium per 24 h infused over 12 h), which can be used even by the youngest children with VDDR2a.

Remarkably, although fractional calcium absorption is low from early childhood through the end of puberty, during and after puberty subjects with VDDR2a develop an unusual adaptation that is characterized by an increase in calcium absorption to levels that are even greater than those of normal subjects.

Accordingly, many affected patients will be able to maintain normal plasma levels of calcium with more modest oral calcium supplementation or, at least in some cases, even without calcium supplements altogether.

### VITAMIN D DEPENDENT RICKETS TYPE2B (VDDR2B)

VDDR2b (OMIM 600785) resembles VDDR2a but is not caused by a defect in the VDR gene. Rather, the molecular defect appears to be overexpression of a nuclear protein that specifically interacts with a DNA response element that binds retinoid X receptor-VDR heterodimers.

This dominant-negative protein appears to be a member of the family of heterogeneous nuclear ribonucleoproteins (hnRNPs), which attenuate gene transcription via their role as hormone response element-binding proteins. (42) have proposed that the vitamin D resistance present in VDDR2b is similar to that described in New World primates. hormone response element-binding protein that leads to target cell resistance to vitamin D as well as other steroid hormones.

No gene has yet been identified as the cause of VDDR2b so it is impossible to state with precision the number of affected subjects. Management of rickets is similar to that described above for VDDR2a.

### VITAMIN D DEPENDENCY RICKETS TYPE3 (VDDR3)

VDDR3 is due to increased inactivation of vitamin D metabolites and is caused by a recurrent gain-of-function missense mutation (p.I301T) in the gene encoding CYP3A4 (44), the most abundant hepatic CYP450 enzyme. The clinical features appear similar to those of patients with VDDR1, but given the small number of reported cases of VDDR3 it may be premature to specify a definitive a description. Both affected individuals had detectable serum concentrations of vitamin D<sub>3</sub> but low serum concentrations of 25(OH)D and 1,25(OH)<sub>2</sub>D that increased after administration of very large doses of vitamin D or calcitriol and which decreased rapidly thereafter. Both patients required high doses of calcitriol or vitamin D<sub>3</sub> (50,000 IU daily) to maintain normal serum concentrations of vitamin D metabolites as well as normal serum levels of PTH, calcium, and phosphorus. In vitro studies of the CYP3A4 p.I301T mutation shows that this enzyme rapidly and extensively inactivates vitamin D metabolites (45), which explains the poor response of affected children to normal doses of vitamin D or vitamin D analogs. These children do respond to parent vitamin D or vitamin D metabolites, but require far greater doses than are necessary in nutritional vitamin D deficiency. They require life long treatment with high dose vitamin D to maintain a biochemical and clinical remission.

## 2. CONCLUSIONS

The biochemical and genetic analyses of various forms of VDDR has yielded important insights into vitamin D homeostasis and 1,25(OH)<sub>2</sub>D action. Similarly, continued study of children and adults with VDDR has the potential to provide a morecomplete understanding of the biological role of vitamin D not only in bone and mineral metabolism but also in other, non-traditional vitamin D actions. The management of VDDR remains a challenge, particularly for treatment of patients with VDDR2, who are often completely resistant to vitamin D andits metabolites. Ongoing studies will be essential to promote the well-being of the families with VDDR and in improving the diagnostic and clinical management of these uncommon genetic disorders.

### AUTHOR CONTRIBUTIONS

All Authors are conceived the topic and wrote the content equally

### Conflict of Interest:

The author declares that the article was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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