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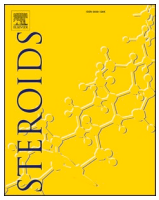

Review

Significance of vitamin D responsiveness on the etiology of vitamin D-related diseases

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ABSTRACT

Vitamin D resistance (VDRES) explains the necessity for higher doses of Vitamin D (VD) than those recommended for treatment success. VD receptor (VDR) signaling blockade, such as that caused by infections and poisons, is one basis for VDRES etiology. Mutations within genes affecting the VD system cause susceptibility to developing low VD responsiveness and autoimmunity. In contrast, VD hypersensitivity (VDHY) occurs if there is extra VD in the body; for example, as a result of an overdose of a VD supplement. Excess 1,25(OH)2D3 is produced in lymphomas and granulomatous diseases. The placenta produces excess $1,25(OH)_2D_3$. Gene mutations regulating the production or degradation of $1,25(OH)_2D_3$ enhance the effects of $1,25(OH)_2D_3$. Increased $1,25(OH)_2D_3$ levels stimulate calcium absorption in the gut, leading to hypercalcemia. Hypercalcemia can result in the calcification of the kidneys, circulatory system, or placenta, leading to kidney failure, cardiovascular disease, and pregnancy complications. The primary treatment involves avoiding exposure to the sun and VD supplements. The prevalence rates of VDRES and VDHY remain unclear. One estimate was that 25%, 51%, and 24% of the patients had strong, medium, and poor responses, respectively. Heavy-dose VD therapy may be a promising method for the treatment of autoimmune diseases; however, assessing its potential side effects is essential. To avoid VD-mediated hypercalcemia, responsiveness must be considered when treating pregnancies or cardiovascular diseases associated with VD. Furthermore, how VD is associated with the related disorders remains unclear. Investigating responsiveness to VD may provide more accurate results.

1. Introduction

A noteworthy development in modern medicine is using vitamin D (VD) to treat and prevent rickets [1,2]. According to estimates, vitamin D deficiency (VDD) affects up to 40 % of people in the European Union and 24 % of Americans [3], and moderate cases of VDD are considered substantial health risks, even though severe cases are rare, and rickets is infrequent. VDD is associated with conditions such as cancer, connective tissue disorders, inflammatory bowel disorders, chronic hepatitis, food allergies, asthma, respiratory infections, and type 1 and 2 diabetes. However, most intervention studies have not proven a link between VDD and these conditions [4]. Calcitriol, a physiologically active VD, mediates its action by binding to the vitamin D receptor (VDR) [5]. VDR is present throughout the body, including in cells involved in immune modulation [6–15]. The almost universal expression of the VDR implies that the VD/VDR axis controls genes associated with several processes, including energy metabolism, immunological responses, cell growth and differentiation, and calcium homeostasis [16]. However, most intervention studies have not proven a link between VDD and these processes [4]. VD supplementation can increase serum $25OHD_3$ concentration to a high normal range. However, this has not been associated with benefits for global health, major diseases, or medical events such as cancer, cardiovascular events, diabetes mellitus, falls, or fractures, at least in largely VD-replete adults [16]. The importance of VD substitution for

Abbreviations: VD, vitamin D; PTH, parathyroid hormone; VDR, vitamin D receptor; VDD, vitamin D deficiency; IIH, idiopathic infantile hypercalcemia; VDRES, vitamin D resistance; VDHY, vitamin D hypersensitivity; IBD, inflammatory bowel disease; MS, multiple sclerosis; DBP, D-binding protein.

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preventing and treating rickets is indisputable. However, treatment results for other diseases associated with VDD and VD are contradictory. This review attempts to determine the effects of VD responsiveness.

1.1. VD metabolism

A review of VD metabolism will help us understand the mechanisms associated with VD responsiveness and the utility of measuring VD metabolites when diagnosing VD responsiveness.

The skin synthesizes cholecalciferol (VD_3), a secosteroid that functions as a prohormone. Although dietary VD supplements can also produce it, endogenous synthesis in the skin is the main source of VD_3. In the skin, UVB causes the phototransformation of 7-dehydrocholesterol into pre-VD_3, and heat promotes the conversion of pre-VD_3 into VD_3. VD_3 is mostly transferred from the skin to the bloodstream by D-binding protein (DBP). Notably, 25-hydroxylases (CYP2R1 and CYP27A1) modify VD_3 via hydroxylation in the liver, resulting in 25-hydroxyvitamin D_3 ($25OHD_3$). Subsequently, 1α-hydroxylase (CYP27B1) performs a second hydroxylation to produce the active form, calcitriol [1,25$(OH)_2D_3$], predominantly in the kidneys. [5] However, hydroxylation can also occur in other tissues and cells. The active form interacts with the VDR and affects biological processes [5,17]. Furthermore, 24-hydroxylase (CYP24A1) converts $25(OH)D_3$ and $1,25(OH)_2D_3$ into inactive metabolites [5]. Additionally, $1,25(OH)_2D_3$ concentration, blood calcium levels, and parathyroid hormone (PTH) levels principally control CYP27B1 and CYP24A1 activity. Furthermore, klotho and FGF23 negatively regulate CYP27B1 and positively regulate CYP24A1, linking VD metabolism to phosphate homeostasis (Fig. 1). [18] Free phosphate is filtered in the glomerulus of the human kidney before being reabsorbed as it travels along the nephron. The sodium phosphate cotransporter (NaPi-IIa), which regulates phosphate reabsorption from primary urine in the proximal tubule, is encoded by SLC34A1. NaPi-Iia, Klotho, FGF23, PTH, and $1,25(OH)_2D_3$ control renal phosphate levels. [19] Intestinal $1,25(OH)_2D_3$ enhances calcium absorption. PTH increases calcium release from the bones into the circulation if the blood-ionized calcium content is low. PTH also accelerates the conversion of $25(OH)D_3$ to $1,25(OH)_2D_3$, which is then released into the bloodstream. PTH prevents phosphate reabsorption, resulting in larger quantities of ionized calcium and lower levels of water-soluble calcium phosphate salts. Consequently, the VD system has a direct feedback mechanism. PTH should be low in the lower third of the reference range if $25(OH)D_3$ levels are physiologically high and vice versa. [20].

1.2. VD resistance and rickets

In the 1930s, some children with rickets were observed to require high doses of VD to alleviate their symptoms. In 1937, Albright, Butler, and Bloomberg introduced the concept of VD resistance (VDRES) [21]. Further research revealed that these children had either hereditary defects in 1α-hydroxylase, leading to decreased active VD (VD-dependent rickets type I [VDDR-I], or congenital defects in VDR. When VDR is defective, genetic VD-resistant rickets (HVDRR), also known as VD-dependent rickets type II (VDDR-II), develops. Both are rare autosomal recessive disorders characterized by hypocalcemia, secondary hyperparathyroidism, and early onset severe rickets. [22] Rare instances of HVDRR defects have been detected to cause this issue. Only 70 items were discussed in the 2007 article "Vitamin D-resistant diseases" [23].

1.3. Acquired form of VD resistance and autoimmune diseases

Although VDRES is rare (see 1.2.), the concept of acquired VDRES has been developed, which is more common and could be related to

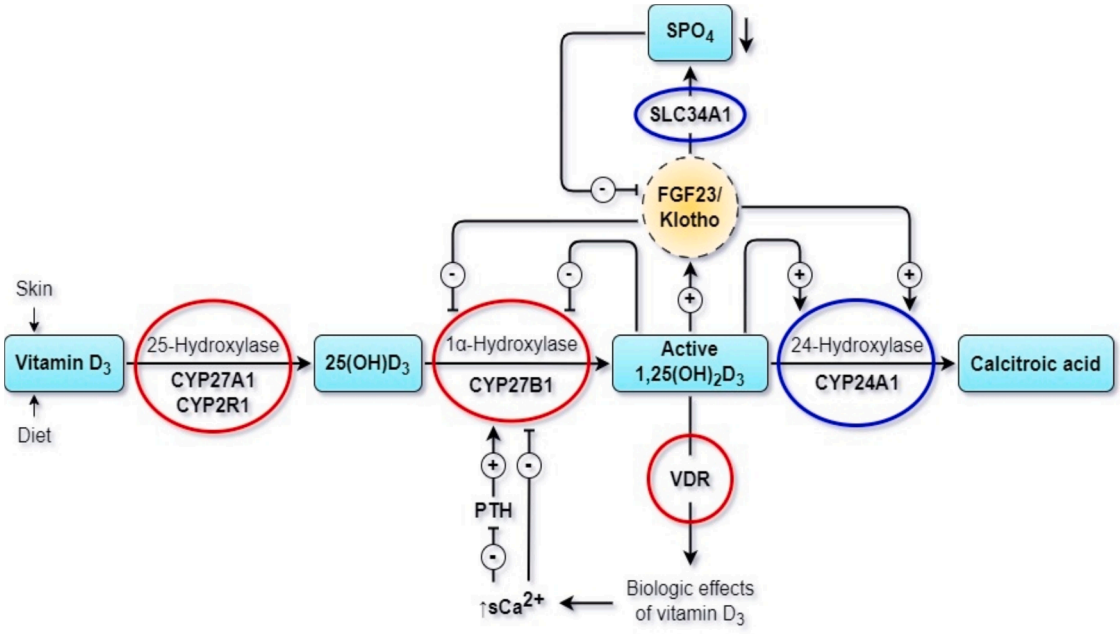

Fig. 1. Vitamin D (VD) metabolism and synthesis. Mutations of the VD pathway. (Glenville Jonesswith the permission of Glenville Jones. The two-step hydroxylation mechanism of VD synthesis and metabolism transforms dietary or skin-produced VD into its active hormonal form, $1,25\text{-}(OH)_2D_3$. VD binds to the vitamin D receptor, controlling the amounts of phosphate and calcium in the serum, which has various biological effects. The enzyme 1-hydroxylase (CYP27B1) is responsible for converting VD into its physiologically active form, $1,25\text{-}(OH)_2D_3$, which is degraded by 24-hydroxylase (CYP24A1). Serum calcium, parathyroid hormone, and $1,25\text{-}(OH)_2D_3$ levels control this process. Additionally, based on phosphate homeostasis, FGF23 affects VD metabolism by restricting the activity of 1,25-(OH)2D3 through the inhibition of 1-hydroxylase (CYP27B1) and activation of 24-hydroxylase (CYP24A1) activity. SLC34A1 regulates proximal tubule phosphate reabsorption from primary urine. Red circles denote proteins in the VD machinery that can cause rickets or autoimmune conditions when mutated. Mutations in CYP24A1 and SLC34A1 can cause nephrolithiasis, hypercalcemia, hypercalciuria, and decreased PTH levels. Hypophosphatemia occurs in patients with SLC34A1 mutations. These mutations are highlighted in blue circles. Renal insufficiency, vascular calcification, and calcification in other organs can result from mutations in the CYP24A1 and SLC34A1 genes.
This figure is adapted from Glenville Jones' article with the permission of Glenville Jones [92]

autoimmune diseases. This resistance results from mutations in the VD system that occur during aging and exposure to environmental factors, thereby impairing VD hormone signaling. These environmental factors include pathogens such as the Ebstein-Barr virus [24], cytomegalovirus [25], legionella, escherichia coli, and Yersinia. [26]. These pathogens can block the VDR and alter host immune responses. Glucocorticoids can also disturb the VDR gene [27]. Aluminum can decrease renal CYP27B1 activity in chickens [28] and has been found at high concentrations in the brain tissue of patients with multiple sclerosis (MS) [29]. Aging reduces intestinal cholecalciferol absorption [30], decreases endogenous skin production [31] and VD hydroxylation [32]. The weakest link in the VD metabolic system is VDR, and the most significant indicators of acquired VDRES are mutations in the VDR [17,20]. The genes CYP2R1, CYP27A1, CYP27B1, and DBP (necessary for VD transport in circulation) and the cell-surface receptor megalin-cubilin, which is the membrane receptor for the $1,25(OH)_2D_3$/DBP complex, also have mutations associated with autoimmune diseases [20].

Autoimmune disorders occur when the immune system mistakenly attacks healthy cells and tissues. VD is vital for maintaining a strong and healthy immune system. Therefore, VDD can increase the risk of autoimmune disorders by weakening the adaptive immune system. [33,34] Several autoimmune conditions such as autoimmune thyroid disease [35], systemic lupus erythematosus [36], rheumatoid arthritis [37], inflammatory bowel disease (IBD) [38,39], MS [43], and insulin-dependent type 1 diabetes mellitus [6] have been associated with VDD. However, more research is needed to determine if VDD is the cause or effect of these autoimmune disorders [33,34]. Patients with IBD often have difficulty absorbing VD, necessitating higher doses of VD to achieve normal serum 25(OH)D levels. This can prevent the development of bone fragility, osteoporosis, and osteomalacia [38]. However, few randomized controlled trials have examined the effects of VD supplementation on disease occurrence and severity. One study found that a higher dose of VD (2000 IU) led to lower levels of proinflammatory markers in children and adolescents with IBD than a lower dose of 400 IU [39]. Children with rheumatic diseases, especially those treated with steroids, are recommended to receive at least double the daily recommended dose of VD for their age (approximately 2000 UI/day) [40].

1.4. High-dose VD therapy

Recent studies on treating autoimmune diseases have revealed the clinical advantages of high-dose VD therapy. A single high dose of VD_3 (100 000 IU) may positively affect health outcomes in older adults [41]. Large-dose, short-term VD supplementation has been shown to reduce insulin resistance compared to placebos in patients with type 2 diabetes [42]. Recommended serum 25(OH)D levels are usually 20 – 30 ng/ mL. In MS treatment, serum 25(OH)D levels of approximately 130 ng/mL are recommended for therapeutic effects. Clinical trials have shown that VD doses ranging from 10,000 to 40,000 IU/day are safe as an add-on therapy. In any case, these trials were relatively short in duration, had small sample sizes, and in many cases, were not placebo-controlled. The adverse effects during the trials were usually minor and manageable. The results of these trials are conflicting, and whether regular VD intake is reasonable beyond the correction of hypovitaminosis D remains unclear. [43].

Dr. Cicero Coimbra, a neurologist from Brazil, used ultrahigh doses of VD to treat patients with autoimmune diseases [44,45]. This approach has been used in Germany to treat patients with autoimmune diseases since 2016. The fundamental idea behind high-dose VD3 therapy is that some patients have a non-hereditary, acquired type of VDRES and insufficient biological activity of $1,25(OH)_2D_3$. To overcome this resistance, high doses of VD_3 are administered to patients to unblock VDRs. The initial doses of VD_3 in the Coimbra protocol depend on the autoimmune disease being treated. For MS, doses of up to 1000 IU of VD_3 per kg of body weight may be used, whereas other autoimmune disorders require smaller doses. [20] In rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, psoriasis, Crohn's disease, and ulcerative colitis, initial VD_3 doses of 300–500 IU/kg of body weight are used. Systemic scleroderma, ankylosing spondylitis, and Hashimoto's thyroiditis require VD_3 doses of 300 IU/kg of body weight, whereas other autoimmune diseases require VD_3 doses of 150 IU/kg of body weight. The doses are gradually adjusted (usually lowered) during follow-up, based on a standardized procedure that considers the patient's clinical condition, calcium levels, and PTH concentrations. [20] Studies have shown that the Coimbra protocol is safe for patients with autoimmune diseases when oral VD_3 is administered in large doses with a strict low-calcium diet and daily fluid intake of 2.5 L. Owing to the underlying VDRES, patients are protected against what is typically considered a potentially toxic dose, and the doses used in this protocol only have physiological effects. [46] The Coimbra protocol is similar to insulin resistance therapy in which higher doses are administered to address resistance [47].

1.5. VD responsiveness range

Carsten Carlberg, a Professor of Biochemistry at the University of Eastern Finland, studied VD's gene regulation and epigenetics. He found that people respond differently, molecularly and biochemically, to the same dosage of VD_3. During the Finnish winter of 2015, 71 senior prediabetic participants in the VitDmet study received daily supplements of 0, 1600, or 3200 IU VD_3. This study focused on the effects of VD_3 supplementation on mRNA expression of 12 VD-regulated genes and several VD-affected laboratory parameters. This study demonstrated that even high doses of VD_3 (3200 IU) did not always have the desired VD-regulatory effects in participants, with 25 % of patients failing to respond as expected. According to this study, patients were categorized as low (24 %), mid (51 %), and high responders (25 %). [48] Later, in 2017, the same research group conducted the VitDbol study, in which a group of healthy students received an 80,000 IU bolus dose of VD_3. The results of the VitDbol study validated the findings of the VitDmet study. [49] To get an acceptable physiological response, such as lowering PTH concentrations or downregulating an activated adaptive immune system, patients with VDRES need substantial doses of VD_3. Increased PTH levels, despite adequate 25(OH)D3 levels, are signs of acquired VDRES and can occur in patients with autoimmune diseases. In the VD system, PTH is essential for improving intestinal calcium absorption, triggering calcium release from the bones, boosting the conversion of $25(OH)D_3$ to $1,25(OH)_2D_3$, and preventing tubular phosphate reabsorption. An average $25(OH)D_3$ level should reduce the PTH levels to the lower third of the reference range. However, this negative feedback loop is disrupted in patients with autoimmune diseases. [20] On the VD responsiveness continuum, individuals with VDRES fall at the low-response end [48,49].

1.6. VD hypersensitivity

Vitamin D hypersensitivity patients (VDHY patients) are on the opposite side of the VD responsiveness continuum. They have either excess VD in the body or their bodies are sensitized to VD Because of this, the effects of VD for them are stronger than average. They don't need as much VD as others. On the other hand, extra sunshine or relatively low therapeutic doses of VD can increase the effects of VD in the body, leading to increased intestinal calcium absorption, calcium mobilization from the bones, and hypercalcemia. [51] The group "VD hypersensitivity" is divided into subgroups "exogenous and endogenous" based on its etiology.

Exogenous VDHY results from consuming extremely large amounts of pharmaceutical VD preparations. Values $>$ 150 ng/mL (375 nmol/L) of serum $25(OH)D_3$ signify exogenous VDHY. The serum $1,25(OH)_2D_3$ levels are average. There is also hypercalcemia and low PTH [52]. According to the 2011 recommendations of the Institute of Medicine, the maximum tolerated levels of VD intake is 1000 IU/d for newborns under

six months of age, 1500 IU/d for infants of six to 12 months of age, 2500 IU/d for children of one to three years of age, 3000 IU/d for children of four–to eight years of age, and 4000 IU/d for adolescents and adults [55]. However, several studies have shown that VD is probably one of the least dangerous fat-soluble vitamins, far less dangerous than vitamin A [56].

Endogenous VD hypersensitivity syndrome was discovered more than 70 years ago. To treat rickets, children are administered high amounts of VD. While the majority of children responded favorably to this treatment, some displayed symptoms of hypercalcemia. This illness spread and became endemic in three distinct occurrences. The first occurred in Great Britain in the early 1950 s [57], the second in Poland in the 1970 s [58], and the third in East Germany in the 1980 s [59]. This syndrome was initially called idiopathic infantile hypercalcemia (IIH), but the name was misleading. It also occurs in adults, and its etiology is well-known.

One cause for endogenous VDHY is ectopic synthesis of 1,25$(OH)_2D_3$. The placenta synthesizes extra 1,25$(OH)_2D_3$ during pregnancy [76]. Sarcoid lymph nodes synthesize extra 1,25$(OH)_2D_3$ [60–62]. Ectopic synthesis of 1,25$(OH)_2D_3$ is also observed in tuberculosis [63], lymphomas [64,65], fungal infections, leprosy, and other granulomatous diseases [51].

Another cause of endogenous VDHY is mutations in the genes responsible for the synthesis or catabolism of VD. In 2011, Shlingmann et al. reported alterations in CYP24A1 expression in patients with idiopathic infantile hypercalcemia (IIH). CYP24A1 catabolizes 1,25$(OH)_2D_3$ into its inactive metabolites. Mutations in the CYP24A1 gene result in the build-up of 1,25$(OH)_2D_3$ and a decrease in its degradation [Fig. 1]. [3,66] In 2017, Schlingmann et al. found that a mutation in the SLC34A1 gene results in hypophosphatemia [4] by impairing the proximal tubules' ability to reabsorb phosphate from primary urine [4,66]. Therefore, hypophosphatemia concurrently inhibits CYP24A1 and stimulates 1α-hydroxylase (CYP27B1) (Fig. 1) [67]. The accumulation of 1,25$(OH)_2D_3$ is also an outcome of this mutation. Nephrolithiasis, decreased PTH levels, hypercalcemia, and hypercalciuria are the hallmarks of both mutations. (Fig. 1) Besides, mutations in SLC34A1 [4,66] cause hypophosphatemia. Other yet unknown abnormalities in the genes controlling VD metabolism are expected, except for in CYP24A1 and SLC34A1 [68].

In addition, an increase in the quantity of VDRs or saturation of the DBP capacity can lead to endogenous VDHY [52].

Endogenous VDHY, caused by gene mutations, constitutes a hereditary risk factor because VD substitution can lead to the development of symptomatic hypercalcemia in otherwise healthy neonates [66]. Biallelic mutations result in the aforementioned clinical and biochemical phenotypes. Individuals carrying monoallelic gene mutations may exhibit hypersensitivity reactions to excess VD, have an attenuated disease, or be asymptomatic carriers [51].

1.6.1. Clinical signs of VD hypersensitivity and hypercalcemia

Clinical signs of hypercalcemia are similar, although the etiology varies [50,54]. Only a small percentage of patients exhibit significant symptoms, and most patients are asymptomatic and diagnosed through routine examinations [51]. In babies, in addition to weight loss, clinical symptoms include polyuria, dehydration, vomiting, and constipation [66].

VDHY may remain undetected until adulthood, and its clinical signs may emerge later in life, particularly in monoallelic mutations. Excessive sun exposure, high-VD food products, or VD supplements can induce increased levels of 1,25(OH)2D3 and hypercalcemia in VDHY patients [51].

Chronic subclinical hypercalcemia and hypercalciuria result in kidney stones, adult renal insufficiency, and severely decreased kidney function. In addition to tubulointerstitial inflammation and fibrosis, mineral deposits associated with nephrocalcinosis play a role in developing end-stage renal diseases [69–72]. Hypertension, arterial calcifications, and arterial vasoconstriction are cardiovascular symptoms associated with hypercalcemia. Mutations in CYP24A1 have been associated with coronary artery calcification, which, in turn, leads to a higher risk of coronary heart disease. [73–75] Throughout pregnancy, the amount of 1,25$(OH)_2D_3$ produced by the placenta increases [76]. Patients with VDHY do not experience an increased VD breakdown. Serious pregnancy consequences include pancreatitis, nephrolithiasis, arterial hypertension, potentially fatal hypercalcemic crises, and lethality for the mother and/or the fetus. [77–81] Additional clinical manifestations of hypercalcemia include neuropsychiatric symptoms such as depression, hallucinations, anorexia, nausea, vomiting, constipation, peptic ulcer disease, pancreatitis, varying degrees of demineralization and fragility of the bone, and stupor and coma in severe cases [51].

Nonetheless, VDHY may remain undetected until adulthood, and its clinical signs may emerge later in life, particularly in monoallelic mutations. Excessive sun exposure, high-VD food products, or VD supplements can induce increased levels of 1,25(OH)2D3 and hypercalcemia in VDHY patients [51].

1.6.2. Diagnosis of VD hypersensitivity

The diagnosis of VD hypersensitivity is challenging. Pregnancy, medication use, VD replacement, and related conditions such as lymphomas, cancer, nephrocalcinosis, granuloma-forming illnesses, and hereditary diseases, as well as nephrolithiasis, decreased PTH levels, hypercalcemia, hypercalciuria, and hypophosphatemia should be carefully considered. In the presence of excessive 25$(OH)D_3$, the resulting hypercalcemia is known as exogenous VDHY. [51] In endogenous VDHY, elevated 1,25$(OH)_2D_3$ concentrations have been associated with hypercalcemia. [51] If pathogenic CYP24A1 mutations are suspected, the 25$(OH)D_3$ to 24,25$(OH)_2D_3$ ratio should be evaluated. The 25$(OH)D_3$ to 24,25$(OH)_2D_3$ ratio is approximately < 30 in most heterozygotes and individuals without pathogenic CYP24A1 mutations; however, it is generally > 80 in individuals with harmful mutations. Genetic testing must be performed if the ratio of 25$(OH)D_3$ to 24,25$(OH)_2D_3$ is > 80. [82,83].

1.6.3. Treatment of VD hypersensitivity

The primary course of hypercalcemia treatment is to reduce calcium intake and consume large amounts of water. Exogenous VDHY necessitates discontinuation of VD supplementation [51]. The central management strategies for CYP24A1 mutations include reducing sun exposure and eliminating VD prophylaxis [3]. For SLC34A1 mutations, phosphate supplementation is the initial therapeutic option; reducing VD consumption does not normalize test findings [4]. Patients with genetic defects that cause hypercalcemia, granulomatous diseases, and lymphomas are advised to avoid exposure to sunlight [52]. Glucocorticoids help reduce calcium levels by reducing intestinal calcium absorption, increasing calcium excretion in the urine, and encouraging the creation of inactive metabolites [52]. Glucocorticoids have no therapeutic effect in individuals with genetic defects that cause hypercalcemia [51]. Patients with CYP24A1 mutations may need to be treated with rifampicin and azoles to treat hypercalcemia. Azole-containing medications are CYP27B1 inhibitors. Rifampicin is a tuberculosis medicine that increases the activity of the enzyme CYP3A4, which, in this case, effectively inactivates VD metabolites compared to CYP24A1. [51].

1.6.4. Prevalence of VD hypersensitivity

The prevalence of VD hypersensitivity remains unknown. A Polish population survey revealed biallelic variations in CYP24A1 and SLC34A1 are found in one in 32,465 births [58]. Severe VDHY is associated with biallelic mutations in the SLC34A1 or CYP24A1 genes [51]. The identification of heterozygous SLC34A1 and CYP24A1 mutations can be challenging. As a result, heterozygous mutations often remain undetected and are not detected until the VD substitution is used. In otherwise seemingly healthy neonates, CYP24A1 or SLC34A1 mutations

are familial risk factors for the development of symptomatic hypercalcemia, which may be exacerbated by VD prophylaxis. Biallelic abnormalities in the CYP24A1 gene may be present in 4–20 % of patients with calcium kidney stones [84]. Sarcoidosis frequently results in VDHY due to the ectopic synthesis of active VD [60]. The frequency of sarcoidosis varies significantly by region, ranging from one to five per 100,000 individuals in South Korea, Japan, and Taiwan to 140–160 per 100,000 individuals in Sweden and Canada [85]. Furthermore, the real-world prevalence of VDHY remains unknown [52]. According to two accurate but narrowly sampled studies, about 25 % of Finns have VDHY [48,49].

The prevalence of new CYP24A1 and SLC34A1 mutations, VD supplementation, and recently identified differences in genes regulating VD metabolism contribute to increased VDHY. The administration of VD_3 at doses higher than those advised may increase the risk of VDHY [51–53].

Table 1 shows the main differences between VD resistance and VD hypersensitivity.

Table 1
Key distinctions between Vitamin D resistance and Vitamin D hypersensitivity.

	VD resistance	VD hypersensitivity
Etiology	Mutations in genes responsible for VD impact on cells (VDR), VD synthesis (CYP27A1, CYP2R1, CYP27B1), or VD transport (DBP) [20]	Inactivating mutations of the CYP24A1 [18] and SLC34A1 [19] genes or mutations of yet unknown genes that affect vitamin D synthesis or catabolism [68] The administration of extremely high levels of VD [49]
	Environmental factors (pathogens, glucocorticoids, toxins) [20]	Granulomatous diseases (e.g. sarcoidosis, tuberculosis), lymphomas [52]
	Aging [30–32]	
	Lack of sunshine [20]	Pregnancy [78]
Diagnosis	PTH elevated $25OHD_3$ average or depressed [20] *	PTH impression [51]
	Ca average or depressed [20]	Hypercalcemia [51] Hypercalciuria [51] Hypophosphatemia (in IIH2) [51] $25(OH)D_3$:$24,25(OH)_2D_3$ → 80 (normal < 30) [51 Increased serum $25(OH)D_3$ → exogenous VD hypersensitivity [52] Increased serum 1,25(OH)2D3 → endogenous VD hypersensitivity [52] Genetic analyses (CYP24A1, SLC34A1) [52]
Associated diseases	Autoimmune diseases, rickets [20]	Calcifications, e.g. in the placenta [78], cardiovascular system [73], and kidneys [71] lead to pregnancy complications, cardiovascular diseases, and kidney diseases
Therapy	High-dose VD therapy? [20]	Stopping VD substitution, avoiding sunshine [52]
Prevalence	Unknown [20]	Unknown [52]

*Values of $25(OH)D_3$ vary among different sources. One estimation is that 25 $(OH)D_3$ concentration < 20 ng/mL; (<50 nmol/L) means VD deficiency and 25 (OH)D concentration of 21–29 ng/mL; [52.5–72.5 nmol/L] means insufficiency [52].

2. Discussion

The treatment of autoimmune diseases can be complicated. High-dose VD therapy may be used to treat VDRES effectively. However, the outcomes and potential negative repercussions must be carefully evaluated.

VD has been shown to help treat or prevent cardiovascular disorders, and VDD has been recognized as a risk factor for these conditions in multiple trials [86]. In contrast, in individuals with VDHY, VD supplementation increases the prevalence of kidney disease and vascular calcification, which are risk factors for cardiovascular diseases [87–90]. Therefore, determining the responsiveness of each patient to VD is essential before treating or preventing cardiovascular diseases using VD.

VDD is believed to increase the risks of pregnancy, and VD supplementation is commonly advised [91]. Nevertheless, in pregnancy, the amount of $1,25(OH)_2D_3$ produced by the placenta increases [76]. Excessive VD production in the placenta, together with VD supplementation, may manifest as symptoms of VDHY, such as hypercalcemia and unfavorable pregnancy outcomes. The VD response can be evaluated using laboratory assays (parathyroid hormone, calcium, phosphate, 25(OH)D3, and 24,25(OH)2D3) performed at the beginning and end of pregnancy. An analysis of the connections between difficulties during pregnancy and VD responses is possible.

Intervention trials have not demonstrated the effectiveness of VD supplementation in treating extraskeletal VD-dependent disorders or a causal relationship between VDD and these diseases. The results of these studies were contradictory. Therefore, considering the VD response in this study may produce more accurate findings.

Given the rarity of inborn resistance or hypersensitivity, administering the recommended amount of VD in neonates is desirable. However, if newborns' growth and development are unsatisfactory, their response to VD needs to be considered.

Few studies concerning the responsiveness to VD have used small sample sizes. Based on these studies, the number of VD-sensitive and −resistant individuals in the population could reach up to 25 % in both groups. Therefore, studies with larger sample sizes are required to assess the importance of VD responsiveness in this population.

3. Closing words

VDD affects people worldwide. On the other hand, the risk of hypercalcemia in individuals with VDHY caused by VD supplementation may increase as more people become aware of the health benefits of VD.

CRediT authorship contribution statement

Ulla M. Järvelin: Writing – original draft, Supervision, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Juho M. Järvelin:** Writing – review & editing, Conceptualization.

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