Focus on Vitamin D and the Adrenal Gland

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Abstract

The main role of vitamin D is to maintain calcium and phosphorus homeostasis, thus preserving bone health. However, recent evidences have demonstrated that vitamin D may also play a role in a variety of nonskeletal disorders such as endocrine diseases and in particular type 1 diabetes, type 2 diabetes, adrenal diseases, and the polycystic ovary syndrome. Despite controversial results on an association of low vitamin D levels with cortisol and aldosterone overproduction, encouraging *in vitro* findings have been reported on vitamin D effects in adrenocortical cancer cells. The focus of this review is the role of vitamin D in adrenal diseases and the results of vitamin D supplementation studies in patients. Although many studies support a beneficial role of vitamin D in adrenal disease, randomized controlled trials and mechanistic studies are required to provide more insight into the efficacy and safety of vitamin D as a therapeutic tool.

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Introduction

The traditional role of vitamin D consists in the regulation of calcium-phosphorus homeostasis and bone metabolism. Recently, several in vivo and in vitro studies recognized various "noncalcemic" effects of vitamin D and its implication in the pathogenesis of diverse conditions, including endocrine diseases [1], autoimmune diseases [2], and cancer progression [3]. Although vitamin D is considered as a steroid hormone, little is known about its adrenal effects and interactions. In particular, a decrease in vitamin D levels has been reported to be associated with excess of both glucocorticoids (GCs) [4–6] and aldosterone [7].

The aim of this review is to highlight the relationship between vitamin D and the adrenal gland, its involvement in adrenal physiology and biochemistry and its correlation with development and progression of adrenal diseases and hormonal excess, such as Addison's disease, Cushing's disease, primary aldosteronism, and adrenocortical tumors.

Vitamin D, Adrenal Physiology and Biochemistry: Shared Chemical Origin and Nuclear Receptor Actions

Although misnamed as vitamin D, the prohormonal compound, calcidiol or $25(OH)D_3$ (25-hydroxyvitamin D3) and the active metabolite, calcitriol or $1,25(OH)_2D_3$ (1,25-dihydroxyvitamin D3), both have endocrine effects through the vitamin D receptor (VDR). Similar to other steroid hormones (gonadal, mineralo- and corticosteroid), the vitamin D compounds act on the nuclear hormone receptor VDR. Moreover, vitamin D, its metabolites and adrenocorticosteroids share a common chemical background: the main precursor for both pathways is 7-dehydrocholesterol. The 7-dehydrocholesterol serves as substrate for further vitamin D3 synthesis through cutaneous UV irradiation whereas other metabolites require different precursors such as ergosterol [8].

One "experiment of nature" has unveiled this mechanism by an inborn error of cholesterol metabolism: a rare genetic disease, Smith-Lemli-Opitz syndrome, is caused by mutations in the DHCR7 (7-dehyrodcholesterol reductase) gene. This gene codes for an enzyme that catalyses the reaction from the precursor 7-dehydrocholesterol to cholesterol. In Smith-Lemli-Opitz syn-

drome, the DHCR7 mutation leads to an accumulation of precursor levels and profound cholesterol deficiency. Patients are also diagnosed with adrenal insufficiency early in life [9]. The mechanism for adrenal insufficiency is put down to defective corticosteroid synthesis that is normally dependent on cholesterol availability. Except for adrenal failure, multiple deficits occur during embryogenesis and the developmental outcome has been described as disappointing [10]. Despite high precursor levels patients appear to have normal 25(OH)D_3 status possibly because they avoid sun exposure due to photosensitivity [11]. Nevertheless this rare syndrome illustrates the close chemical relationship of vitamin D and adrenocorticosteroid metabolism through their chemical origins (**Fig. 1**).

Vitamin D levels are influenced by environmental (food, supplementation, UV-exposure) as well as genetic factors. Out of the 4 genes regulating vitamin D levels that have been identified in genome wide association studies (GWAS), DHCR7 is one of the key genes [12]. Furthermore, DHCR7 haplotypes have been described to be under balancing selection and thus have adapted to evolutionary pressures in early human migration to Northern latitudes [13]. This observation illustrates that the vitamin D pathway belongs to one of the key biological processes of human development.

The most important link between vitamin D and adrenal steroidogenesis is the recently discovered vitamin D response element in the promoter of *CYP21A2*, the gene encoding the 21-hydroxylase [14]. The active vitamin D metabolite 1,25 $(OH)_2D3$ can thereby downregulate the expression of the 21-hydroxylase required for glucocorticoid and mineralocorticoid synthesis. The group had earlier demonstrated a suppression of steroidogenesis by downregulation of *CYP21A2* and upregulation of *CYP11A1* and *CYP17A* using 1,25$(OH)_2D_3$ in a human adrenocortical cell line model (NCI-H295R) [15].

Besides the shared chemical origin between the 2 steroid pathways vitamin D may be actively metabolized by the adrenal gland allowing a paracrine action. *In vitro* studies have shown that adrenocortical cells from female Wistar rats or the mitochondrial fraction from bovine adrenal glands may secrete vitamin D metabolites and the human adrenal glands has a high gene expression of *CYP27A1* and *CYP2R1* [16]. This suggests an adrenal specific vitamin D activation pathway. In addition the adrenal gland may hydroxylate to metabolites 20(OH)D2,

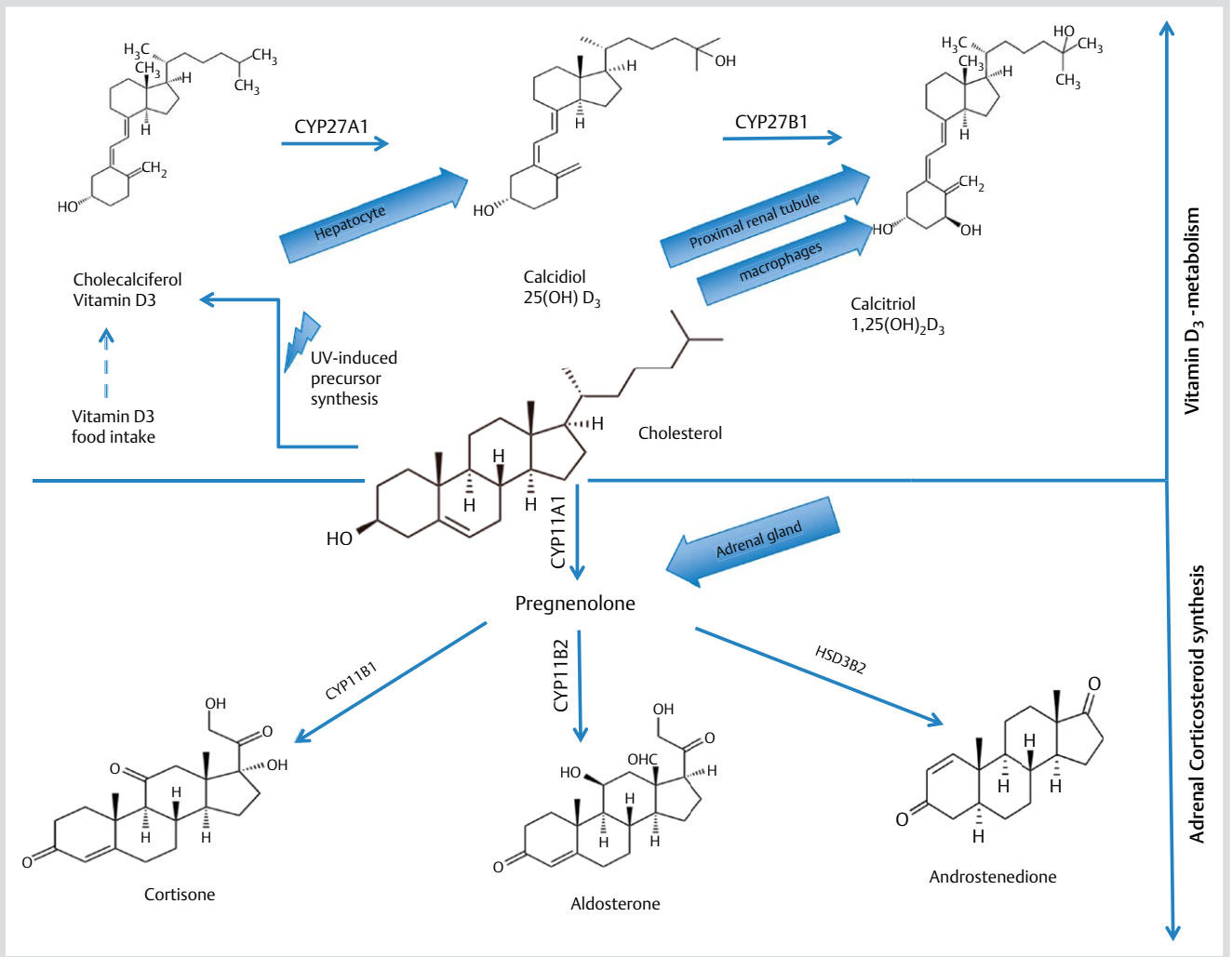

Fig. 1 Simplified biochemical paths for vitamin D and adrenal steroid production: 7-dehydrocholesterol is the common precursor for both vitamin D synthesis and adrenal corticosteroid hormone secretion. Whereas the precursor 7-dehydrocholesterol is catalyzed by 7-dehyrodcholesterol reductase to cholesterol and under UV-irradiation further processed to cholecaciferol, then to 25D3 in the liver (CYP27A1, CYP2R1, CYP3A4, CYP2J2) finally activated by CYP27B1 in proximal tubules of the kidney or by macrophages to 1,25$(OH)_2D3$ (upper part). Adrenal corticosteroid synthesis occurs in 3 different zones to gluco-, mineralocorticoid, and adrenal androgen synthesis. (Color figure available online only).

17,20$(OH)_2$D2, and 1,20$(OH)_2$D2 similar to placentas as signs of *CYP11A1* activation [17]. Earlier it had been shown by biochemical experiments on pig and rat adrenal tissue homogenates that transformation from steroid precursors such as 7-dehydrocholesterol into vitamin D metabolites is abundant and can be blocked by adrenal specific enzyme inhibition [18].

In addition, the adrenal is capable of converting 25$(OH)D_3$ to the most active metabolite 1,25$(OH)_2D_3$ by the 1-α-hydroxylase encoded by *CYP27B1* [16]. Thus, it is conceivable that local conversion may lead to disease specific paracrine effects in the adrenal tissue that would go unnoticed by measuring plasma levels of vitamin D. The biological significance of these active vitamin D derivatives has yet to be determined, but may help to explain why the adrenal glands is better protected from autoimmune attack in comparison to other endocrine glands as can be seen by the low incidence of this rare disease [19].

VDR Expression on Adrenal Cells and Alternative Routes of Vitamin D Action

The classical vitamin D action occurs via the nuclear receptor VDR through domain specific ligand binding and heterodimerization with Retinoid X receptor (RXR). Whereas the expression of VDR by RT-PCR has been demonstrated in human adrenocortical tissue [20], evidence of protein expression by immunofluorescence is not clear for the normal adrenal cortex and may depend on the developmental stage, immune stimulation, and specific changes induced by macrophages [21]. Alterations of VDR expression thereby depend on the cellular environment, exposure to cytokines, and growth factors.

Besides the classical VDR-RXR heterodimer binding in many tissues, there is evidence for the binding of vitamin D metabolites to retinoid acid-related orphan receptors (ROR) in several layers of the skin [22]. This illustrates that vitamin D metabolites have not only an endocrine but also a para- or autocrine potential.

Furthermore, several reports have appeared that support the concept of an alternative pathway for vitamin D action that is independent from the nuclear VDR. The main observation for this concept is that transgenic VDR –/– mice show biological vitamin D effects on chondrocytes and calcium mobilization from gut cells – despite the absence of the VDR – indicating alternative signaling pathways. One membrane component for this rapid vitamin D effect cascade is Pdia3 (membrane-associated protein disulfide isomerase, family A, member 3) [23]. This rapid action pathway involves downstream mediators such as phospholipase A2 activating protein (PLAA), Src activation and calmodulin-dependent protein kinase II (CaMKII) in bone cells but has not yet been studied in other cells [24].

Vitamin D and Addison's Disease

Addison's disease (AD) is a rare condition characterized by autoimmune mediated destruction of the three hormone producing cell layers of the adrenal cortex resulting in either isolated adrenal deficiency or as part of an autoimmune polyendocrine syndrome. Although the etiology of Addison's disease is largely elusive, current concepts suggest that a combination of genetic and environmental factors leads to destructive CD8-T-lymphocytic infiltration of the adrenal cortex and subsequent antibody production to the adrenocortical antigen 21-OHase [25].

The main genetic susceptibility for Addison's disease is conferred by the HLA locus [26,27], but also other genes located on the long arm of chromosome 12, belonging to the vitamin D pathway (such as *VDR* and *CYP27B1*) have been associated with AD [28–31]. In this context, analysis of four single nucleotid polymorphisms (SNPs) in the *VDR* gene (Fok I, Bsm I, Apa I, and Taq I) in 220 controls and 95 patients with AD from Germany revealed that both "ff" genotype of Fok I and "tt" genotype of Taq I were significantly more frequent in disease patients (odds ratio 2.75 and 2.42, respectively). Although this initial observation has not been confirmed in other populations, it provided the basis for elucidating the vitamin D pathway in Addison's disease [28]. Further studies were carried out in Germany (320 controls and 124 patients with AD), United Kingdom (464 controls and 104 patients with AD), and Poland (251 controls and 101 patients with AD), which investigated one SNP situated in the promoter region of the *CYP27B1* gene (−1 260) where the frequency of CC genotypes was significantly higher in patients [29–31]. Also the concomitant autoimmune disorders showed an association of the C (−1 260) allele with polyendocrine cases of AD [30]. Additionally, extended haplotype analysis within the *CYP27B1* gene performed by Jennings et al. [31] found the haplotype T (−1 918) C (−1 260) G (−1 077) to be more frequent in AD (75.8 %) subjects than in control individuals (66.7 %).

The shared genetic association of vitamin D pathway genes in other autoimmune endocrine diseases (e.g., T1DM) [32] and the identification of vitamin D system components by diverse methodologies in the adrenal gland [33–36] – both cortex and medulla – as well as in immune cells [37], provide evidence that the vitamin D system is involved in the pathophysiology of this immune mediated disorder.

Whether 25$(OH)D_3$ concentrations differ specifically in patients with autoimmune Addison's disease is currently under investigation. There is evidence of interaction between the vitamin D status and predisposing gene loci similar to findings in T1DM [38]. However, the implication of the vitamin D deficiency for AD susceptibility was recently described by Ramagopalan et al. [39]. They observed a significantly elevated frequency of diverse autoimmune diseases including AD in 13260 patients with a vitamin D deficiency who had been admitted to a UK hospital. Vitamin D deficiency may predispose to AD by perturbing the immune response. Alternatively the inflammatory process leading to it may result in vitamin D deficiency. However, in AD, glucocorticoid deficiency may lead to suppression of the parathyroid hormone-vitamin D axis [40] suggesting a connection between vitamin D and adrenal steroidogenesis.

In this context, it has been reported that an adequate glucocorticoid substitution in AD patients normalizes the calcium level and restores the production of 1,25$(OH)_2D_3$ [41,42]. It is important to note that high turnover osteoporosis, which is characterized by a reduced bone mineral density (BMD), results in secondary adrenal insufficiency after long substitutive therapy with glucocorticoids. In addition, it has been demonstrated in AD patients that the BMD can be increased using a combined treatment with calcitriol and calcitonin [43].

AD patients often report about chronic fatigue, muscle weakness, and reduced energy despite optimized corticosteroid supplementation. Since vitamin D may improve muscle function [44] its supplementation may improve quality of life in chronic AD. In summary, preliminary evidence suggests that vitamin D modifies genetic susceptibility to Addison's disease and also its metabolic state. However, much remains to be elucidated on its

functional and clinical relevance, in particular whether vitamin D supplementation in chronic AD has beneficial effects and if so through which mechanisms.

Vitamin D and Cushing's Syndrome

The data about effects of glucocorticoid (GC) excess on vitamin D metabolism is controversial. Previous studies reported that chronic excess of GC decreased [4,45–47], increased [5,48,49] or did not change [6,50–52] plasma levels of $25(OH)D_3$ or $1,25(OH)_2D_3$. Klein et al. [4] documented lower concentration of serum $25(OH)D_3$ during GC excess using a radioligand assay. They reported that GC dose and $25(OH)D_3$ concentration were inversely related. Similar results were described by Seemam et al. [45] who found a small but significant decrease in plasma $25(OH)D_3$ and $1,25(OH)_2D_3$ concentration while no changes were detected in rates of production and degradation of $1,25(OH)_2D_3$. Interestingly, the authors described a more important decrease in $25(OH)D_3$ levels in patients with endogenous Cushing's syndrome, which may be due to the longer duration of exposure to chronic GC excess. These results were confirmed in a recent study by Chaiamnuay et al. [47], which examined the prevalence of vitamin D deficiency in Thai patients with systemic lupus erythematosus (SLE). The authors described a high prevalence of vitamin D deficiency (<30 ng/ml) and insufficiency (<20 ng/ml), in 41% and 17%, respectively, of SLE studied patients despite many of them taking vitamin D supplements. They showed that a higher current daily GC dose was associated with lower serum $25(OH)D_3$ levels. In contrast, Findling et al. [5] reported similar plasma $25(OH)D_3$ and $1,25(OH)_2D_3$ levels in patients with endogenous ACTH-dependent Cushing's syndrome compared to controls. However, they demonstrated lower $1,25(OH)_2D_3$ levels in all patients with remission of disease and suggested that chronic endogenous hypercortisolism may result in a small but significant increase in vitamin D activation. They speculated that this increase of $1,25(OH)_2D_3$ may be due in part to the changes in phosphate homeostasis, because they did not find a correlation with PTH levels. Instead, Kugai et al. [48] showed that patients with endogenous Cushing's syndrome with marked osteopenia had higher levels of $1,25(OH)_2D_3$ compared to patients without osteopenia and normal controls. They attributed it to an increased calciuria that in turn stimulated PTH secretion and thus $1,25(OH)_2D_3$ synthesis. A slight increase of $1,25(OH)_2D_3$, without change in $25(OH)D_3$ levels, was shown also by Hahn et al. [49] in healthy adults after short term prednisone administration (20 mg/day for 2 weeks) even as intestinal calcium absorption decreased. The authors concluded that the reduced intestinal calcium absorption after GC administration cannot be ascribed to decreasing vitamin D metabolites in the circulation. In slight contrast to these results, Jackson et al. [50] assessed the potential antagonism between GC and vitamin D in volunteers, hypoadrenal subjects on cortisone and calciferol as well as in subjects with Cushing's syndrome on calciferol. Hereby, adrenal dysfunction did not influence vitamin D levels. Aloia et al. [6] reported normal $25(OH)D_3$ concentration in patients with both endogenous and exogenous hypercortisolism. They hypothesized that – if GC affects vitamin D metabolism – it must be at one biochemical step beyond the conversion of vitamin D3 to 25-hydroxycholecalciferol. The controversial results found in the literature about the relationship of GC excess with vitamin D may due to heterogeneity of the subjects, the nature of the underlying disease, the dose and duration of GCs excess, and/or the degree of disordered bone mineral metabolism.

Recently, Corbee at al. [52] demonstrated in dogs with pituitary-dependent hypercortisolism that $1,25(OH)_2D_3$ level did not change after hypophysectomy, also in comparison to control dogs. The authors concluded that there was no need for vitamin D supplementation before and after the treatment of this disease. Similar results in animals were obtained by Jiang et al. [53] after administration of high dose dexamethasone in rats. They did not report alteration in vitamin D levels after GC administration, but showed the decreased expression of both VDR and the cytochromes P450 enzymes involved in its activation (CYP27B1) and catabolism (CYP24A1) in brain and myocardium. The authors supposed the potential involvement of vitamin D in the neural and cardiac dysfunctions induced by GC excess.

Excess of GC causes negative calcium balance and progressive bone loss [54]. Vitamin D supplementation has been analyzed as a potential therapy because it regulates calcium homeostasis by increasing intestinal calcium absorption and renal reabsorption [55]. Several studies showed the efficacy of vitamin D plus calcium supplementation in maintaining bone mineral density and reducing vertebral fracture risk in patients treated with GCs [56,57]. The American College of Rheumatology recommended a supplementation with 800–1 000 IU/d (20–25 g/d) of vitamin D [58]. Recommendations from The Endocrine Society suggested higher levels of supplementation, proposing that patients using GCs required 2–3 times more vitamin D than healthy individuals of the same age [59]. A recent meta-analysis [60] that collected a total of 25 studies with 867 participants, demonstrated that adults receiving GC treatment for different diseases had suboptimal serum calcidiol concentrations (range 16–24 ng/ml) for the prevention or management of osteoporosis, compared to steroid-untreated controls. This effect of GC on the vitamin D status should also be correlated to GC excess induced obesity that led to the sequestration of vitamin D in body fat depots, thus decreasing its viability [59–61].

In the report by Chaiamnuay et al. [47], SLE patients had a high prevalence of vitamin D deficiency and insufficiency although more than half of them were vitamin D supplemented. Summarizing these observations, we hypothesize that patients with chronic exposure to GC excess, both endogenous and exogenous, require higher doses of vitamin D supplementation. Chronic steroid medication is one factor in the algorithm for therapy decisions in osteoporosis, which requires at least a minimal vitamin D supplementation [62–64].

Vitamin D and Adrenocortical Tumors

Epidemiological data have shown that sunlight exposure and subsequent increased circulating levels of $25(OH)D_3$ are associated with reduced prevalence and mortality in different types of cancer [65–68]. Furthermore, several *in vitro* studies have demonstrated that exposure of tumor cells to high concentrations of vitamin D compounds inhibited their proliferation and induced differentiation [69–71]. The main oncologic model systems investigating the relationship with vitamin D have been so far prostate cancer, breast cancer, melanoma, and colorectal cancer [65,68–71]. Few studies have investigated adrenocortical tumors (ACTs): Pilon et al. [20] demonstrated the presence of

VDR at both mRNA and protein levels in normal adrenal glands and ACTs. They showed a higher expression of VDR in adrenocortical adenoma (ACA) than in carcinoma (ACC) with a particularly strong immunohistochemical cytoplasmatic staining of VDR in cortisol-producing ACA. This may reflect the loss of VDR-mediated protection by malignant transformation of ACC cells, as reported in other cancer types [72]. Besides, the authors investigated the antiproliferative effects of vitamin D in ACC tumor cells model. They showed that treatment with $1,25(OH)_2D_3$ increased the percentage of NCI-H295R cells in G0/G1 phase, while the cells in phase S decreased. This block of transition from G1 to S cell phase that resulted in a decrease of proliferating cells did not affect the rate of apoptosis. Absence of apoptosis after exposure to $1,25(OH)_2D_3$ has also been observed in other cell types [73, 74].

The effect of vitamin D on steroidogenic genes and adrenal hormone production has been assessed in the human NCI-H295R ACC cell line [15]. Lundqvist et al. [15] demonstrated that the treatment with $1,25(OH)_2D_3$ significantly decreased the production of corticosterone, DHEA and androstenedione levels by up to 50%, whereas aldosterone levels slightly decreased. They explained these results through the alteration of mRNA expression of genes coding for steroidogenic enzymes. In particular, they showed suppressed levels of *CYP21A2* mRNA and an overexpression of *CYP17A1* mRNA in the ACC cell line after treatment with vitamin D. The downregulation of *CYP21A2* caused the decrease of aldosterone and corticosterone biosynthesis. Cortisol levels were not significantly decreased probably due to the opposing effect of *CYP17A1* overexpression. Despite the higher *CYP17A1* mRNA expression and the corresponding 17α-hydroxylase activity after vitamin D administration, the biosynthesis of androgenic steroids (DHEA, DHEAS and androstenedione) was downregulated in these ACC cell lines. The authors explained this discrepancy via decreased 17,20-lyse activity of CYP17A1 after $1,25(OH)_2D_3$ treatment. Other steroidogenic enzymes, such as CYP11B1, CYP11B2, and 3β-HSD, were not altered by $1,25(OH)_2D$ (**Table 1**).

There are no in vivo studies on the relationship between vitamin D and ACC. An important topic for further research would be the effect of mitotane, the most important drug for the treatment of ACC patients, on vitamin D levels. Mitotane inhibits adrenal steroid synthesis and adrenocortical cell proliferation through undefined mechanisms. Mitotane is a strong inducer of CYP3A4 [75], one of the most important enzymes of the family of drug-metabolizing cytochrome P450. P450 is implicated in the metabolism of about 50% of all drugs [76]. The induction of CYP3A4 during mitotane treatment causes a rapid metabolization of different drugs with consequent reduction of their clinical efficacy [77]. Since CYP3A4 is also involved in the vitamin D metabolism [78] it may accelerate vitamin D catabolism and contribute to vitamin D deficiency in patients affected by ACC. However, further basic and clinical studies are necessary to investigate the relationship between vitamin D and mitotane.

Table 1 Effect of vitamin D on steroidogenic genes and steroid biosynthesis in the NCI-H295R ACC cell line.

Enzyme altered by $1,25(OH)_2D$ treatment	Effect in gene expression	Effect on steroid biosynthesis
CYP21A2	↓ mRNA levels	↓ corticosteroid
		↓ aldosterone
CYP17A1	↑ mRNA levels	↓ DHEA
	↑ 17α-hydroxylase activity	↓ DHEAS
	↓ 17,20-lyse activity	↓ androstenedione

Vitamin D and Primary Hyperaldosteronism

Primary hyperaldosteronism (PHA) is caused by aldosterone producing adrenal tumors or adrenal hyperplasia (APA). Several studies demonstrated that aldosterone excess may also impact on bone mineral homeostasis, with consequent hypercalciuria and secondary hyperparathyroidism [79]. Many studies investigated the role of vitamin D in patients with PHA, even if the results about vitamin D levels in PHA patients were controversial [7, 79–83]. In the Graz Endocrine Causes of Hypertension (GECOH) study, Pilz et al. [80] reported similar $25(OH)D_3$ concentrations in patients with PHA and essential hypertension (EH). They found lower serum calcium and higher plasma parathyroid hormone (PTH) levels in PHA patients compared with EH, and hypothesized that aldosterone excess may decrease serum calcium levels and thereby contribute to secondary hyperparathyroidism. The major limitation of this study is the small sample size of PHA patients (n = 5 APA and n = 5 idiopathic hyperaldosteronism). In a cross-section comparison in 105 patients studied by Maniero et al. [81], there were no differences in vitamin D levels between PHA and EH patients. Similarly deficient levels of $25(OH)D_3$ were observed in both groups even if vitamin D treatment did not fully correct the hyperparathyroidism in PHA patients. The authors speculated that vitamin D deficiency is unlikely to explain the hyperparathyroidism seen in PHA in comparison to EH patients. Similar results were described by Ceccoli et al. [82] which studied 116 patients with PHA compared to 110 EH patients. In line with earlier data, they reported higher PTH and lower serum calcium with no differences in vitamin D concentration in PHA patients compared to EH patients. Moreover the authors demonstrated no change in vitamin D levels in PHA patient before and after adrenalectomy or medical treatment, despite an improved bone mineral density (BMD) after treatment. Salcuni et al. [83] described elevated PTH levels associated with higher 24-h urinary calcium excretion and similar vitamin D levels in PHA patients compared to patients with adrenal incidentaloma without aldosterone excess. The main findings on PTH and calcium levels in PHA patients compared to EH patients were confirmed by Petramala et al. [7]. In contrast to previous studies, Petramala et al. showed lower vitamin D serum levels in PHA patients and a more frequent vitamin D deficiency (< 20 ng/dl) in these patients compared to those with EH. Vitamin D deficiency associated with PHA was first described in a patient by Nguyen et al. [84] in 2006. This was an important feature in a patient with PHA, because the hypovitaminosis D may lead to a reduced bone mass, a significant increase in renal calcium loss and increased levels of PTH, typically found in osteomalacia [7]. Due to the lack of unifying results to support the role of vitamin D as a potential treatment for PHA, the supplementation with vitamin D should be only reserved for patients with PHA that have hypovitaminosis D.

Although vitamin D seems to play a role in secondary hypertension, that is PHA, it has been reported to have a probable role in the pathogenesis of essential hypertension. In vitro and in vivo studies reported that $25(OH)D_3$ levels may influence blood pressure by functioning as an endogenous inhibitor of the renin-angiotensin system (RAS) [85, 86], interacting with sodium, calcium and RAS to modulate vascular smooth muscle tone

[87,88], and indirectly affecting the vascular endothelium [89–91]. Controversial results were reported in more than 20 cross-sectional studies that examined the association between vitamin D levels and either blood pressure or prevalent hypertension [92]. Although most of these studies demonstrated that low levels of vitamin D (<30 ng/ml) are associated with a higher blood pressure, hypovitaminosis D remains to be established as a risk factor for hypertension. Vitamin D supplementation studies failed to demonstrate an antihypertensive effect of vitamin D, thus requiring further controlled studies [92].

A recent mendelian randomization analysis [93] which studied a large sample size (up to n = 108 173 individuals from 35 studies) provided evidence for a causal effect of low vitamin D levels on higher blood pressure and risk of hypertension. One of the limitations of that study was that only associations of vitamin D with blood pressure and hypertension were analyzed whereas the risks of other disease outcomes in the same patients (e.g., diabetes) were neglected. However, these findings permit further investigations in an independent, similarly powered study, to investigate the necessary vitamin D doses and appropriate target groups for the prevention or treatment of hypertension.

Conclusions

Several observations suggest that vitamin D may play a role of in the pathogenesis of adrenal diseases. However, due to the paucity of prospective intervention and nonintervention studies, the results of ongoing and future trials need to be taken into careful consideration before any evidence-based recommendations can be made. Currently only guidelines for glucocorticoid-induced osteoporosis recommend vitamin D supplementation, but in other adrenal disorders individual medical decisions are necessary to justify such treatment. Advancing knowledge in the vitamin D field needs to be observed for additional diagnostic or therapeutical applications in adrenal diseases.

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Conflict of Interest

The authors declare that they have no conflicts of interest in the authorship or publication of this contribution.

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