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Vitamin D status and its associations with clinical and laboratory parameters in patients with Addison's disease

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Abstract: Introduction: There is increasing evidence that several autoimmune diseases, as well as their activity, are associated with vitamin D (VD) deficiency. Our study aimed to evaluate the prevalence of VD insufficiency in patients with Addison's disease (AD), as well as to evaluate associations between VD concentrations and various clinical and laboratory parameters of the disease.
Materials and Methods: We retrospectively analyzed medical records of 31 adult patients diagnosed with autoimmune Addison's disease, in whom serum VD was measured. We assessed correlations between serum VD and various clinical and laboratory parameters.
Results: 90.3% of AD patients had inadequate VD concentrations (<30 ng/mL), and 19.3% of them were found to be severely VD deficient (<10 ng/mL). Among assessed laboratory variables, only serum calcium concentrations significantly correlated with VD status ($r = 0.53$, $p = 0.006$). The mean serum VD concentration was significantly lower in patients with severe fatigue (15.17 ± 8.41 vs 26.83 ± 12.29 ng/mL, $p = 0.011$) and limited exercise capacity (12.38 ± 6.9 vs 21.63 ± 10.87 ng/mL, $p = 0.016$).
Conclusions: This study demonstrates a high prevalence of VD deficiency in AD patients, as well as the association between low VD concentrations with symptoms such as severe fatigue or limited exercise capacity. Further studies are needed to clarify if impaired VD status is a risk factor in the pathogenesis of AD and to assess if VD supplementation improves the quality of life of AD patients.

Keywords: primary adrenal insufficiency, Addison's disease, vitamin D, autoimmunity.

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Introduction

Vitamin D (VD) is a steroid hormone, which is mainly produced in the skin during sun exposure and has a crucial impact on calcium and phosphate metabolism as well as bone mineralization. Recently, extra-skeletal actions of VD are emphasized, as it may influence the function of the cardiovascular system, carcinogenesis, or immunity [1–4]. It has been proven that different immunocompetent cells, such as macrophages, dendritic cells, T cells, and B cells, express VD receptors that may respond to the biologically active forms of vitamin VD [5]. VD and its deficiency have been increasingly associated with autoimmune diseases, for instance, type 1 diabetes mellitus, rheumatoid arthritis, and systemic lupus erythematosus [6–8]. Several studies across the globe have also revealed that VD deficiency influences the activity (including laboratory indicators) of autoimmune diseases [9, 10].

Addison's disease (AD), also known as primary adrenal insufficiency, is a rare endocrine entity. The most common cause of AD is autoimmune adrenalitis [11]. The etiology of this process is complex and is impacted by genetic, immunological, and environmental factors. It has been proven that all forms of autoimmune adrenalitis show some association with specific gene variants of the major histocompatibility complex (e.g. HLA-DR3) or genes involved in immune-regulatory mechanisms (e.g. CTLA-4) [12]. 1.25-dihydroxyvitamin-D_3 inhibits the production of inflammatory cytokines and promotes the development of regulatory T cells expressing CTLA-4 and FoxP3 [13]. Additionally, VD receptor and VD activating enzyme 1-alpha-hydroxylase are expressed in various immune cell types and have a crucial impact on proliferation, differentiation, and cytokine production by antigen-presenting and adaptive immune cells [14].

Our study aimed to evaluate the prevalence of VD insufficiency in patients with Addison's disease, as well as correlations between VD concentrations and the various clinical and laboratory features of the disease.

Materials and Methods

Patients and study design

We retrospectively analyzed medical records of 90 consecutive patients hospitalized diagnosed with primary adrenal insufficiency in the Department of Endocrinology, Jagiellonian University Medical College in Kraków between January 2013 and December 2019. Patients with autoimmune Addison's disease with measured serum VD concentrations were included in the study. The diagnosis of AD was established by documented hypocortisolemia associated with raised serum adrenocorticotropic hormone (ACTH) and typical symptoms. Autoimmune etiology of the disease was con-

firmed by positive autoantibodies against 21-hydroxylase. Patients with other than autoimmune etiologies of adrenal insufficiency (tuberculosis, systemic mycoses, an acquired immunodeficiency syndrome, neoplastic disease, and use of drugs that reduce the synthesis of adrenal cortex hormones (mitotane, aminoglutethimide, ketoconazole, metyrapone, etomidate)) and hospitalized for the adrenal crisis were excluded. Previous use of vitamin D supplements was not an exclusion criterion. Finally, data from 31 patients were entered into this study.

Laboratory assessment

All laboratory measurements analyzed in this study were performed in the Clinical Biochemistry Department of the University Hospital in Krakow using ROCHE Cobas® 6000/8000 platform, except for total VD which was assessed on ROCHE Cobas® e411 platform. Parathormone (PTH), VD, cortisol, ACTH, Dehydroepiandrosterone sulfate (DHEA-S) concentrations were measured by electrochemiluminescence (ECLIA). Serum calcium was measured by the colourimetric o-cresophtalein complex method in an alkaline environment, inorganic phosphates — by ammonium phosphomolybdate method. ROCHE Eclesys® total vitamin D II assay determines serum concentration of $25(OH)D_3$ and has been validated by the LC-MS/MS method (manufacturer's data). The Clinical Biochemistry Department has been certified by the Randox International Quality Assessment Scheme (RIQAS), the Unity Interlaboratory Comparison Program, the Sysmex International Quality Assurance System, and the StandLAB IQS.

VD status was determined by measuring total serum $25(OH)D_3$ concentration, which is the dominant circulating form of VD. Based on the Endocrine Society guidelines [15]: VD deficiency was defined as 25-hydroxyvitamin D3 concentrations <20 ng/mL; VD insufficiency was defined as concentrations ranging from 20 to 29.9 ng/mL, and vitamin D sufficiency as a VD of 30–100 ng/mL. We also defined severe vitamin D deficiency as serum VD concentrations <10 ng/mL.

Data collection

The following anthropometric, demographic, and clinical data were collected from electronic medical records: age, sex, weight, height, body mass index (BMI), smoking status, and comorbidities (hypothyroidism, Hashimoto's thyroiditis, Graves' disease, type 1 diabetes mellitus, type 2 diabetes mellitus, arterial hypertension and hyperlipidemia). Daily doses of hydrocortisone, fludrocortisone, and dehydroepiandrosterone during hospitalization and data on previous VD supplementation were also recorded. The clinical data regarding the patients' symptoms had been collected from structured medical interviews carried out during admission to the hospital.

All the subjects with AD were asked by the attending physician whether any of the following symptoms had occurred within four weeks prior to admission to the hospital: severe fatigue, fainting, limited exercise capacity, loss of appetite, weight loss, nausea, vomiting, diarrhea, musculoskeletal or abdominal pain. Severe fatigue was defined as a subjective symptom including reduced psychomotor drive. The study was approved by the Jagiellonian University in Kraków local ethics committee (No 1072.6120.135.2020) in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

Statistics

Descriptive statistics (mean, standard deviation for quantitative variables, and frequency and percentage for categorical variables) was used to characterize patients with AD. Shapiro-Wilk test was used to check for normal distribution of data. Student's t-test was used for normally distributed quantitative data and U Mann-Whitney test for variables with a non-Gaussian distribution.

Relationships between VD concentrations and patients' demographic data, laboratory markers and daily doses of medications were determined using the Spearman rank correlation coefficient. One-way analysis of variance was used to determine if the VD concentration depends on the season. All data were analyzed with StatSoft Statistica v. 13 (StatSoft Inc., Tulsa, OK, USA). P values <0.05 were considered significant.

Results

The study population comprised 31 patients, 80.6% of whom were females and 19.4% males. Their age ranged from 18 to 72 years, with a mean age of 44.2 ± 14.6 years. Twelve (38.7%) patients presented with an isolated AD. Sixteen (51.6%) subjects had Hashimoto's thyroiditis, two patients suffered from type 1 diabetes, and one patient had Graves' disease. The included AD patients did not have other autoimmune diseases than those mentioned above. All the patients received hydrocortisone (15–60 mg/day) as glucocorticoid replacement, eighteen were supplemented with fludrocortisone (0.05–0.1 mg/day), and four — with dehydroepiandrosterone (5–25 mg/day). The characteristics of the study group are presented in Table 1.

The mean serum VD concentration in the study group was 18.1 ± 9.95 ng/mL. 90.3% of the subjects had inadequate VD concentration — 54.8% below 20 ng/ml and 35.5% between 20 to 30 ng/ml, respectively (Fig. 1). Furthermore, 19.3% of patients have been found to be severely deficient in VD (<10 ng/mL) and in two subjects, the VD concentration was below the limit of detection (<3 ng/mL). Overweight and obese AD patients (BMI >25 kg/m^2) had a lower VD concentration (16.3 ± 8.73 ng/mL) compared to patients with normal BMI (19.85 ± 10.96 ng/mL), the difference was not

Table 1. Baseline characteristics of study participants.

	AD patients
N	31
Age (years)	44.2 ± 14.6*
Female (%)	80.6
BMI (kg/m^2)	23.3 ± 5.4*
Former smoker, n (%)	7 (22.6)
Current smoker, n (%)	4 (12.9)
Serum calcium (mmol/L)	2.39 ± 0.13*
Serum phosphate (mmol/L)	1.24 ± 0.19*
Plasma parathormone (pg/mL)	38.6 ± 20.7
Vit. D supplementation, n (%)	10 (32.3)
Hypothyroidism, n (%)	23 (74.2)
Hashimoto's thyroiditis, n (%)	16 (51.6)
Graves' disease, n (%)	1 (3.3)
Type 1 diabetes mellitus, n (%)	2 (6.5)
Hypogonadism, n (%)	1 (3.3)
Arterial hypertension, n (%)	4 (12.9)
Type 2 diabetes mellitus, n (%)	5 (16.1)
Hyperlipidemia, n (%)	9 (29)

* mean ± SD

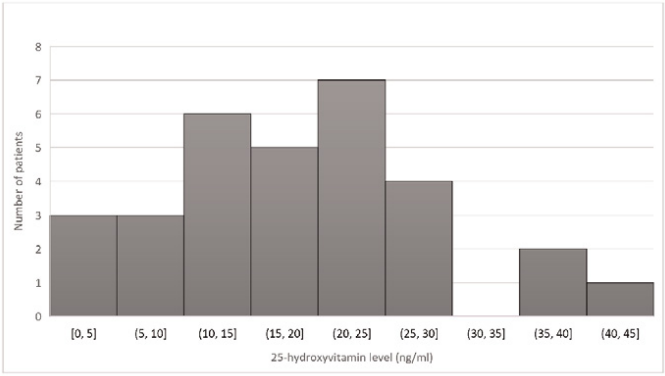

Fig. 1. Distribution of serum vitamin D concentrations in patients with Addison's disease.

statistically significant (p = 0.33). There were no significant associations of serum VD concentration with sex, age, and smoking status. The VD concentration did not differ between patients with autoimmune polyendocrine syndrome type 2 and patients with autoimmune adrenalitis as an isolated disorder (17.06 ± 7.8 vs 19.64 ± 12.53 ng/mL, respectively; p = 0.49).

Ten patients (32.25%) supplemented 2000 IU vitamin D prior to the admission to the hospital; however, in 70% of them, supplementation did not provide an adequate VD concentration. There was a significant difference in VD concentration between patients previously supplementing and non-supplementing VD (23.91 ± 3.6 vs 15.29 ± 1.77 ng/mL, p = 0.02). No significant linkage was observed between VD concentration and a sezon (p = 0.24).

The correlations between serum VD concentrations and laboratory and clinical variables are presented in Table 2. Only serum calcium concentrations correlated significantly with VD status (r = 0.53, p = 0.006).

Table 2. Correlations of serum vitamin D concentrations with clinical and laboratory variables in patients with Addison's disease.

Variable	Correlation coefficient	*p* value
Age (years)	–0.04	0.84
BMI (kg/m^2)	–0.05	0.80
Serum calcium (mmol/L)	0.53	0.006
Serum phosphates (mmol/L)	–0.22	0.35
Plasma parathormone (pg/mL)	0.04	0.88
Morning serum cortisol (measured 8.00 a.m.) (μg/dL)	–0.42	0.11
Plasma ACTH (ng/L)	0.137	0.54
Serum DHEAS (μmol/L)	0.12	0.63
Hydrocortisone daily dose (mg)	0.03	0.86
Fludrocortisone daily dose (mg)	–0.12	0.53
Dehydroepiandrosterone daily dose (mg)	0.13	0.54

Correlations were determined with the Spearman rank correlation coefficient.

We did not find any association between VD status and hydrocortisone (r = 0.127, p = 0.5), fludrocortisone (r = 0.07, p = 0.693) or dehydroepiandrosterone daily dose (r = 0.75, p = 0.251).

The most commonly reported symptom was severe fatigue, which occurred in 78.6% of patients (Table 3). The mean concentration of serum VD was significantly lower in patients with severe fatigue than in those without that symptom (15.17 ± 8.41

vs 26.83 ± 12.29 ng/mL, p = 0.011). Also, patients with limited exercise capacity had significantly lower VD concentrations than subjects with no such limitations (12.38 ± 6.9 vs 21.63 ± 10.87 ng/mL, p = 0.016). No association was found between serum VD concentrations and other clinical features.

Table 3. Frequencies of reported symptoms and vitamin D concentrations in patients with Addison's disease.

	Frequency of the clinical symptom (%)		**Serum vitamin D (ng/mL)***	***p* value**
Severe fatigue	78.6	Absent	26.83 ± 12.29	0.011
		Present	15.17 ± 8.41	
Fainting	17.9	Absent	18.55 ± 10.59	0.34
		Present	13.62 ± 8.86	
Limited exercise capacity	42.9	Absent	21.63 ± 10.87	0.016
		Present	12.38 ± 6.9	
Loss of appetite	32.1	Absent	19.35 ± 9.59	0.258
		Present	14.11 ± 11.51	
Weight loss	46.4	Absent	19.82 ± 8.68	0.243
		Present	15.18 ± 11.82	
Nausea	17.9	Absent	17.53 ± 11.21	0.88
		Present	18.3 ± 5.38	
Vomiting	17.9	Absent	17.67 ± 11.2	0.99
		Present	17.63 ± 5.56	
Diarrhea	14.3	Absent	17.41 ± 11.02	0.76
		Present	19.19 ± 5.05	
Musculoskeletal pain	46.4	Absent	19.02 ± 12.22	0.46
		Present	16.1 ± 7.82	
Abdominal pain	25	Absent	17.1 ± 11.16	0.62
		Present	19.37 ± 7.8	

*mean ± SD

Discussion

Vitamin D deficiency has been found to be associated with autoimmune disorders, such as Hashimoto's thyroiditis, type 1 diabetes mellitus, systemic lupus erythematosus, multiple sclerosis or rheumatoid arthritis [9, 16–19]. Moreover, $1.25(OH)_2D_3$, the

most active vitamin D metabolite, effectively prevents the development of autoimmune diabetes mellitus [20] and autoimmune thyroiditis in animal models [21]. VD has a multifactorial impact on the human immune system — it regulates T and B cell function, plays a role in developing resident tissue macrophages, inhibits T helper 1, T helper 17 lymphocytes and dendritic cell differentiation as well as has the ability to inhibit the expression of human leukocyte antigen (HLA) class II on cells [5].

The autoimmune process is currently the most common cause of primary adrenal insufficiency in developed countries [22, 23]. The strongest genetic associations with AD were found within some HLA class II alleles [24, 25]. Several disease-susceptibility alleles have been described, including three loci associated with T and B cell-associated activation and differentiation (MHC, CTLA4 and PTPN22) [26].

On the other hand, very little is presently known about environmental factors in the pathogenesis of AD. VD deficiency may impact the clinical aspects of Addison's disease. VD deficiency could lead to immune dysfunction which promotes releasing inflammatory cytokines such as interleukin-1, tumor necrosis factor α and interferon α. It was observed that among patients with systemic lupus erythematosus and with low serum VD, interferon-induced genes were overexpressed in peripheral blood mononuclear cells, which in turn correlated with more active disease. A similar correlation between the proinflammatory cytokines activity and low serum VD level was found in multiple sclerosis, rheumatoid arthritis, type 1 diabetes and inflammatory bowel disease [27]. Moreover, VD supplementation has been shown to have an immunomodulatory effect by regulating late-activated T cells and monocytes in AD patients [28].

Thus, better insight into the interplay between VD and the autoimmune process destroying the adrenal cortex should contribute to knowledge about the pathomechanisms of AD.

At present, there is a lack of studies assessing VD concentrations in patients with Addison's disease. To the best of our knowledge, this study would be the first attempt to investigate the relationship between VD concentrations and clinical and laboratory parameters in adult AD patients.

Our analysis showed that 90% of investigated patients with primary adrenal insufficiency had inadequate vitamin D status. Furthermore, 70% of the patients who had been supplementing 2000 IU of VD per day were also either VD insufficient or deficient, highlighting the need for a higher dose of VD supplements to boost the VD status.

A small randomized crossover trial on 13 patients with AD revealed that three months of treatment with cholecalciferol dose of 4000 IU/d provided sufficient $25(OH)D_3$ concentrations and resulted in a reduction of peripheral blood-derived late-activated Th cell percentages as well as late-activated Tc cell percentages. Notably, the response of Th and Tc cells to VD supplementation was significantly associated

with two single nucleotide polymorphisms in the CYP27B1 gene and VD receptor gene, so we can suppose that AD patients may respond differently to VD treatment depending on their genetic background [28].

A study by Pani *et al.* suggested that VD receptor gene polymorphisms appear to be associated with susceptibility to Addison's disease, demonstrating that the "ff" genotype of the FokI restriction digestion pattern (indicative of polymorphism rs10735810) of the VD receptor gene and the "tt" genotype of the TaqI restriction digestion pattern polymorphism (rs731236) of the VD receptor gene were significantly more frequent in AD patients than in the control group [29]. The gene *CYP27B1*, which encodes 25-hydroxyvitamin-D-1α-hydroxylase [30], has also been implicated as being associated with AD [31, 32].

In 54.8% of patients in our study, Addison's disease occurred as part of autoimmune polyendocrine syndrome type 2 (APS-2). Patients with APS-2 had insufficient VD status, but the VD concentration was not different from that of patients with isolated AD. Our findings are in agreement with the study by Bellastella *et al.*, which demonstrated that patients with APS-2 presented lower concentrations of $25(OH)D_3$ in comparison to healthy controls, but the VD status was not different in patients with single or multiple autoimmune diseases [33].

Our analysis revealed that among laboratory measurements, only serum calcium had a statistically significant correlation with VD status. This finding is also consistent with the study by Penna-Martinez *et al.*, in which VD supplementation led to non-significant changes in phosphate and parathormone concentrations but increased the serum calcium to the normal range [28].

In our research, severe fatigue was the most common reported complaint (78.6% of patients).

Interestingly, we observed a significantly lower serum VD concentration in patients with severe fatigue than in subjects without this symptom. Several theories have been proposed to explain the relationship between vitamin D supplementation and reduced fatigue. First, the VD receptor is broadly expressed in the brain, including neurons and glial cells. Interestingly, VD also regulates the release of nerve growth factor, which is essential for survival of hippocampal and cortical neurons. In particular, VD receptors and CYP27B1 expression are most abundant in the dopaminergic neurons within the substantia nigra [34]. Thus, one of the major factors that may contribute to low VD related fatigue is altered dopamine level [35]. Serotonin is also one of the major players in fatigue. Specifically, the altered central serotonin to dopamine ratio contributes to increased fatigue [36]. VD regulates serotonin pathways in the central nervous system by inducing the expression of tryptophan hydroxylase, the enzyme catalyzing the synthesis of serotonin from tryptophan [37].

Adequate vitamin D levels also promote remodeling of skeletal muscle cells. VD has been shown to have a profound effect on mitochondrial oxygen consumption and

mitochondrial dynamics [38]. VD promotes mediators of mitochondrial biogenesis and fusion, such as MYC, MAPK13, optic atrophy protein 1 and endothelial PAS domain-containing protein 1 mRNA [39]. VD receptor expression and its activation in human muscle tissue may also induce protein synthesis in muscle. In addition, a growing body of research has showed positive effects of VD supplementation on muscle strength in healthy individuals [40].

Several studies showed that increasing $25(OH)D_3$ concentrations may have a beneficial effect on fatigue in autoimmune disorders such as systemic lupus erythematosus [41, 42] as well as multiple sclerosis [43]. The double-blind, randomized placebo-controlled trial also revealed that VD supplementation among otherwise healthy VD-deficient individuals with fatigue led to a significant improvement in that symptom in the VD-supplemented group compared with the placebo group [44]. That is why we suppose that VD supplementation could decrease fatigue and improve the well-being of AD patients.

Additionally, we observed that patients with decreased exercise capacity had significantly lower VD concentrations than those without this symptom ($p = 0.016$). However, the question arises whether VD deficiency makes individuals more susceptible to low exercise tolerance, or it is just a consequence of the disease that AD patients spend less time outdoors.

Our data confirm previous results that showed decreased physical activity and increased fatigue in patients with AD [45, 46]. Despite optimized therapy with glucocorticoids and mineralocorticoids, AD patients have a reduced quality of life compared to healthy individuals. The most often reported complains, persistent fatigue and low physical activity, could have a detrimental impact on the increased mortality rate from cardiovascular disease, which is twofold higher in AD patients compared with the general population [47–49]. The impact of VD supplementation on AD patients' quality of life needs to be established.

Study limitations

The total number of subjects studied was limited, and the low sample size in our study may be insufficient to find associations with more clinical or laboratory measurements, because of the lack of statistical power. However, Addison's disease is a rare disorder, with incidence rates of 5–6 per million per year [50, 51]. Due to its relative rarity, it is almost impossible to perform a prospective study.

Another limitation of our study is that we did not compare the adequate VD concentration group and the group with insufficient and deficient VD in demographic characteristics and clinical manifestations of the AD. However, this was impossible as only three subjects in our study had an adequate VD concentration.

Due to the retrospective design, our study did not include factors such as dietary calcium intake or sun exposure. Furthermore, in the group which supplemented VD before the admission to the hospital, the duration of VD supplementation was not recorded. Other unnoted factors include time-varying hormonal levels, especially serum cortisol, which vary throughout the day and a single morning measurement may not reflect the function of the adrenal cortex.

Another important limitation of the retrospective design is that the study cannot show a causation effect — we could not conclude whether low VD contributes to fatigue and limited exercise capacity or vice versa. Also, we did not use validated tools such as quality of life questionnaires. Finally, we collected data regarding patients symptoms (e.g. fatigue or fainting) from the medical charts in our hospital database; therefore, the quality of these findings rely on accurate medical charting. We also did not take into account confounding factors which might influence symptoms reported by patients. For example, a subjective feeling of severe fatigue may also result from old age or from the coexistence of Hashimoto's disease [52].

Despite these limitations, we believe that our study has contributed to the knowledge on vitamin D status in AD patients. Further studies on a larger group of AD patients are required to better understand the role of VD in primary adrenal insufficiency.

Conclusions

In summary, our study is the first report investigating VD concentrations and their associations with clinical and laboratory variables in patients with Addison's disease. We observed a very high incidence of VD deficiency in those patients. Low concentrations of VD have been associated with increased fatigue and decreased exercise capacity. Supplementation with VD may improve the quality of life of patients with Addison's disease, however further, preferably prospective, studies are needed to understand the role of VD in the therapeutic approach to autoimmune primary adrenal insufficiency.

Author contributions

Study design: K.Z. Data collection: K.Z., K.M., M.T.M., G.S. Data analysis: K.Z. Data interpretation: K.Z., K.M., G.S., M.T.M. Drafting manuscript: K.Z., K.M. Revising manuscript content: K.Z., M.T.M., G.S., A.S., A.H.D. All authors revised the paper critically for intellectual content and approved the final version. All the authors vouch for the accuracy and completeness of the data. All authors agreed to submit the manuscript for publication.

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Disclosure

The authors have nothing to declare.

Conflict of interest

None declared.

Abbreviations

AD — Addison's disease
APS-2 — autoimmune polyendocrine syndrome type 2
VD — vitamin D

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