

# Ultraviolet Radiation, Vitamin D and Autoimmune Disorders

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*It is widely acknowledged that excessive sun exposure increases the risk for cutaneous cancer, while excessive photoprotection is associated with inadequate vitamin D synthesis. Suboptimal values of vitamin D are a risk factor for numerous dermatological disorders. Therefore, a balance between photoprotection and sun exposure is required to assure normal development of the organism. Decrypting the mechanisms through which vitamin D intervenes in the pathogenesis of autoimmune disorders is the objective of numerous ongoing studies. Identifying the vitamin D deficiency in patients with autoimmune disorders could be used in establishing early treatment and preventing the progression of the disorder.*

*Keywords: ultraviolet radiations, vitamin D, autoimmune disorders, alopecia areata, inflammation*

Sun exposure increases cutaneous synthesis of vitamin D. Several studies, but not all, suggest that low levels of vitamin D in the blood are associated with photocarcinogenesis, premature skin ageing, psoriasis, vitiligo, autoimmune disorders. Numerous current investigations are directed towards identifying the molecular mechanisms through which vitamin D might influence the occurrence and development of alopecia areata.

Alopecia areata is a chronic, hair specific, autoimmune disorder. It is a common form of nonscarring alopecia occurring in genetically predisposed patients. However, environmental factors like stress, hormones, diet or infection, among others, have also been incriminated. It has a prevalence of 0.1%-0.2% in population. It can occur at any age but the onset of the disorder is usually in the first three decades of life. It is the most common form of alopecia in children. It affects males and females equally. It is associated with other autoimmune disorders like myxedema or Hashimoto's thyroiditis, pernicious anemia, type I diabetes mellitus, vitiligo [1,2,3].

The autoreactive CD8+T-cells play a major role in the pathogenesis of the disorder. The healthy human hair follicle bulb has an immunological privilege during the anagen growth phase because the major histocompatibility complex (MHC) class I and class II molecules are not expressed while TGF- $\beta$ , IGF-1 and MSH- $\alpha$  are overexpressed. In alopecia areata however MHC I and MHC II molecules are strongly expressed and allow the interaction between CD8+T cells and MHC I presented autoantigens. Immunosuppressive molecules are decreased while adhesion molecules are overexpressed, thus leading to perifollicular inflammation. Melanocyte associated autoantigens might be a target of the autoaggressive T-cells [1, 4, 5].

The debut of the disease is usually sudden. Patients present round or oval patches of hair loss. The initial lesion is bald and smooth in the center and can present short hairs in the periphery of the patch. Those are easily removed and are called exclamation mark hairs because their distal end is broader than the proximal end (1,3,6). Cadaver hairs are also present. They represent hairs which break before reaching the surface of the skin and appear as black dots. The patches usually have normal appearing

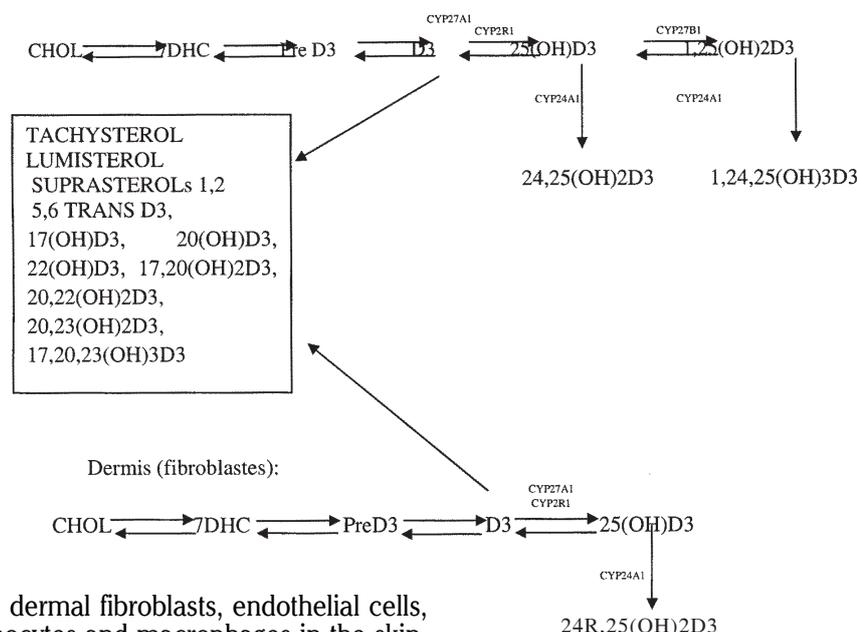
skin but erythema can also occur in some cases. Patients can have one or several lesions which can coalesce. Sometimes patients can lose all the hair on their scalp- alopecia totalis- or even all the hair on their body- alopecia universalis. Ophiasis, a band-like loss of hair along the periphery of the temporal and occipital scalp, is associated with a poor prognosis (1,2,3). The scalp is the most frequent location but the eyebrows, eyelashes, beard, as well as virtually any area with hair, can be affected. Interestingly, the pigmented hairs are preferentially affected and therefore, in patients with grey hair, a sudden change in hair color can occur when the disease is rapidly progressing. In the regrowth phase the hairs are initially hypopigmented and fine but they usually become normal in time [1,2].

The histopathological examination is not mandatory but when it is performed it shows peribulbar lymphocytic inflammation affecting the anagen follicles at the margin of the patches or the follicles in the early catagen phase. Therefore, there is a large number of catagen and telogen follicles. When the disease is more evolved the hair follicles start to decrease in size and are situated more superficially, in the mid or lower dermis[2,7].

Skin cells are equipped with biological systems which assure the synthesis and catabolism of vitamin D (3). The following were identified in the skin: vitamin D-25OHase (CYP27A1), 25OHD-1 $\alpha$ OHase (CYP27B1), 1,25(OH)<sub>2</sub>D-24(OH)ase (CYP24A1), vitamin D receptor (VDR). After UVB (290-315nm) exposure, cholesterol (CHOL) is successively transformed into 7-dehydro-cholesterol (7DHC), provitamin D (PreD3), vitamin D (D3). Vitamin D does not have a significant biological value. Vitamin D can be transformed into suprasterols 1,2 and 5,6 trans vitamin D (5,6 transD3), photoproducts involved in the proliferation and regulation of epidermal differentiation. Excessive synthesis of vitamin D in the skin is prevented by photosensitive conversion of vitamin D into tachysterol and lumisterol, biologically inactive components. Through hydroxidation reactions, vitamin D is transformed into 25(OH)D<sub>3</sub> (25-hydroxy vitamin D<sub>3</sub>) and 1,25(OH)<sub>2</sub>D<sub>3</sub> (1,25-dihydroxy vitamin D<sub>3</sub>), biologically active compounds (8-18). In vitro, and, highly probable, in vivo, other hydroxylated vitamin D compounds are obtained in the skin, via CYP11A1. Of those, we mention: 17(OH)D<sub>3</sub> (17-hydroxy

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vitamin D<sub>3</sub>, 20(OH)D<sub>3</sub> (20-hydroxy vitamin D<sub>3</sub>), 22(OH)D<sub>3</sub> (22-hydroxy vitamin D<sub>3</sub>), 17,20(OH)<sub>2</sub>D<sub>3</sub> (17,20-dihydroxy vitamin D<sub>3</sub>), 20,22(OH)<sub>2</sub>D<sub>3</sub> (20,22-dihydroxy vitamin D<sub>3</sub>), 20,23(OH)<sub>2</sub>D<sub>3</sub> (20,23-dihydroxy vitamin D<sub>3</sub>), 17,20,23(OH)<sub>3</sub>D<sub>3</sub> (17,20,23-trihydroxy vitamin D<sub>3</sub>). Some of these hydroxylated compounds of vitamin D promote the immune response, the inflammatory response, cellular differentiation and apoptosis and inhibit angiogenesis, proliferation, metastasation [8,9,15,16,18]



In keratinocytes, dermal fibroblasts, endothelial cells, immune cells, monocytes and macrophages in the skin, vitamin D interacts with VDR (vitamin D receptor) and RXR (retinoic X receptor). This complex binds to the DNA through VDREs sequences (vitamin D response elements) and promotes the transcription and repression of numerous genes involved in the cutaneous physiopathology [8,10,15,16,18].

The objective of this study is to investigate the processes and mechanisms through which vitamin D<sub>3</sub> could affect the occurrence and evolution of alopecia areata. In order to achieve this objective we followed: the measurement of serum values of vitamin D<sub>3</sub> in patients with alopecia areata as compared to the control group and the evaluation of the statistical relation between the serum vitamin D<sub>3</sub> and immuno-inflammatory factors.

## Experimental part

### Method and materials

49 patients with alopecia areata and 88 healthy volunteers, with the same geographic background, were included in this prospective observational study. The inclusion criteria for the study were: adult persons, female/male ration 1.3, sufficient sun exposure, adequate nutritional status, non-smokers, normoponderals, normal levels of the serum calcium, calciuria, serum phosphate, alkaline phosphatase, parathormone. The exclusion criteria were: pregnancy, alcoholism, drug use, systemic treatments, metabolic, cardiovascular, endocrine, renal, hepatic disorders, cancer, other autoimmune disorders, infections. All the participants signed a consent form for the use of the biological samples in this prospective study, approved by the hospital's Ethics committee.

For the identification and quantification of vitamin D<sub>3</sub> numerous analytical methods were elaborated, of which we specify: thin-layer chromatography, UV/VIS absorption spectrophotometric methods, HPLC (high-performance liquid chromatography), LC-MS/MS (liquid chromatography-mass spectrometry), CLIA (Chemiluminescence Immunoassay), ELISA (enzyme-linked immunosorbent assay), EIA (enzyme immunoassay), RIA (radioimmunoassay). In this study the quantitative determination

of 25-OH vitamin D from the human serum was determined through the use of Euroimmun ELISA kit (with a sensitivity of 1.6 ng/mL for 25-OH vitamin D<sub>3</sub>) and through chemiluminescence (with a detection limit of 4 ng/mL). The results were not affected by 24,25 (OH)<sub>2</sub> vitamin D<sub>3</sub>, vitamin D<sub>2</sub> (ergocalciferol), vitamin D<sub>3</sub> (cholecalciferol).

The quantitative determination of C-reactive protein, ceruloplasmin and transferrin was performed with the immunoturbidimetric method and the determination of the albumin was done through photometry (Human reagents).

The hematologic, biologic, serologic evaluations of the study participants were done through standardized analysis methods, using automatic systems.

The statistical process was performed with the specialized program SPSS. The following statistical tests were used: t, Anova, Pearson correlation coefficient, statistical significance level 0.05.

## Results and discussions

The basic characteristics of patients with alopecia areata and controls, expressed through the mean value and mean standard deviation, are presented in table 1. No statistically significant differences between the studied groups were registered regarding serum concentrations of glucose, urea, creatinine, lipids, triglycerides, cholesterol, bilirubin, aminotransferases, calcium, alkaline phosphatase, phosphor, PTHi, albumin, transferrin. The serum values of CRP, ceruloplasmin, 25(OH)D<sub>3</sub>, determined in patients with alopecia areata and control, presented statistically significant differences between the two monitored groups (table 1).

CRP concentration was significantly higher in patients with alopecia areata as compared to control ( $0.88 \pm 0.51$  mg/dl versus  $0.13 \pm 0.55$  mg/dl, CI=95%,  $p < 0.05$ ) (table 1 and table 2). The basal levels of CRP in patients with alopecia areata were situated in the reference domain in 42.8% of cases and in 57.2% of the cases pathological levels were recorded. In the control group, 95.4% of the cases are situated in the reference domain established by the producer of the analysis kit (fig. 1).

Parameters	Alopecia areata	Control	p significance
Glycemia(mg/dl)	83.2±12.1	79.8±9.4	NS
Urea(mg/dl)	31.2±8.3	28.4±6.4	NS
Creatinin(mg/dl)	0.62±0.08	0.71±0.05	NS
Lipids (g/dl)	626.3±29.2	601.6 ±37.1	NS
Triglyceride (mg/dl)	79.2±11.9	83.4±16.6	NS
Cholesterol (mg/dl)	163.3±22.6	159.0±18.3	NS
Bilirubin (mg/dl)	0.26±0.07	0.19±0.08	NS
AST (U/L)	18.3±4.3	17.1±5.2	NS
ALT(U/L)	16.8±6.8	18.7±3.9	NS
Calcemia (mg/dl)	8.24±0.30	8.76±0.24	NS
Calcemia (mg/dl)	8.24±0.30	8.76±0.24	NS
Alkaline phosphatase (U/L)	238.1±29.3	209.7±23.1	NS
iPTH (pg/ml)	28.3±8.3	31.0±8.7	NS
Phosphor (mg/dl)	3.6±0.7	3.4±0.6	NS
CRP (mg/dl)	0.88±0.51	0.13±0.55	<0.05
Ceruloplasmin(mg/dl)	38.4±4.2	33.7±1.9	<0.05
Albumin(g/dl)	3.68±0.66	4.10±0.92	NS
Transferrin (mg/dl)	198.1±48.3	241.4±42.5	NS
25(OH) D3 (ng/ml)	14.3±10.7	26.8±14.4	<0.05

AST: aspartate aminotransferase; ALT: alanine aminotransferase; CRP: C reactive protein; PTHi: parathormon intact; 25(OH)D3 : 25-hydroxy vitamin D3; NS: insignificant statistic.

**Table 1**  
GENERAL COMPARISON BETWEEN  
ALOPECIA AREATA AND CONTROL

Significance	CRP (mg/dl)	Alopecia areata (n)	Control (n)
Optimal level	<0.60	21	84
Upper norm	>0.60	28	4

**Table 2**  
COMPARISON OF SERUM CRP IN  
ALOPECIA AREATA AND CONTROL.

Significance	Ceruloplasmin(mg/dl)	Alopecia areata (n)	Control (n)
Optimal level	30.0-36.0	11	83
Upper norm	>36	38	5

**Table 3**  
COMPARISON OF SERUM  
CERULOPLASMIN IN ALOPECIA  
AREATA AND CONTROL

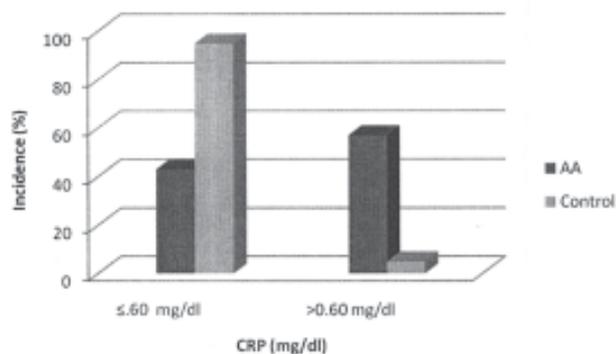


Fig. 1 CRP levels at patients with alopecia areata (AA) and control

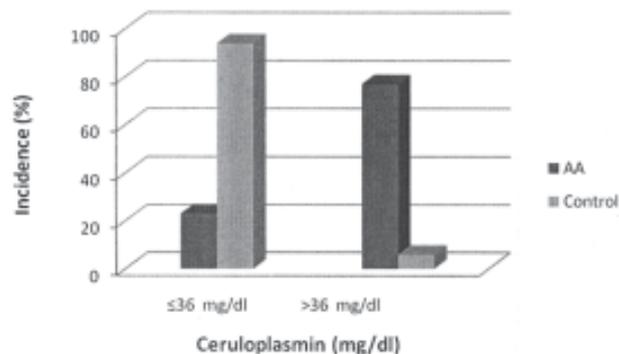


Fig. 2. Ceruloplasmine levels at patients with alopecia areata (AA) and control

High levels of serum ceruloplasmin were obtained in patients with alopecia areata as compared to the control (38.4±4.2 mg/dl versus 33.7±1.9 mg/dl, CI=95%, p<0.05) (table 1 and 3). Levels situated in the reference domain were obtained in 22.5% of cases with alopecia areata and in 77.5% significantly high levels were obtained. In controls,

most serum values of ceruloplasmin (95.0%) are lower than 36.0 mg/dL (fig. 2).

Normal levels of albumin were obtained in 40% of alopecia areata cases, and in 60% of cases low levels were obtained. In control, over 92.0% of the cases presented normal values for serum albumin and in 8.0% low levels

Significance	Albumin(g/dl)	Alopecia areata (n)	Control (n)
Optimal level	>3.5	19	81
Suboptimal values	<3.5	30	8

**Table 4**  
COMPARISON OF SERUM ALBUMIN IN  
ALOPECIA AREATA AND CONTROL

Significance	Transferrin (mg/dl)	Alopecia areata (n)	Control (n)
Optimal level	>200	27	86
Suboptimal values	<200	22	2

**Table 5**  
COMPARISON OF SERUM TRANSFERRIN IN  
ALOPECIA AREATA AND CONTROL

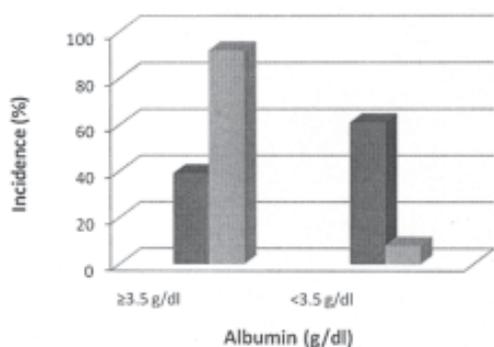


Fig. 3. Albumin levels at patients with alopecia areata (AA) and control

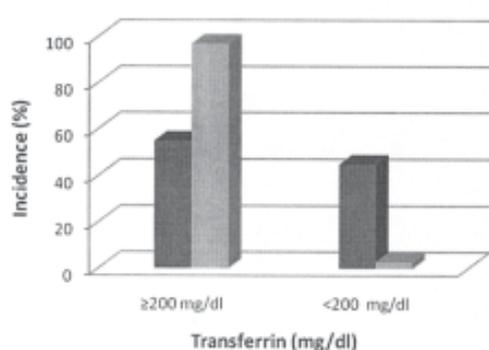


Fig. 4. Transferrin levels at patients with alopecia areata (AA) and control

were obtained (fig. 3). Even though the mean values for the serum albumin were different in the two analyzed groups, no statistically significant differences were recorded between alopecia areata and control (table 3 and table 4).

Normal values for serum transferrin were obtained in 55.1% of cases with alopecia areata and low levels were obtained in 44.9%. In the control group, 98% of the analyzed cases presented levels higher than 200 mg/dL serum for transferrin (fig. 4). Statistically, no significant differences were obtained for serum transferrin between patients with alopecia areata and controls (table 1 and 5).

Currently, there is no consensus on the optimal values of 25(OH)D3 in our country. For the analysis of experimental data, in this study, we chose samples of population from various geographical areas, comparable with regard to the demographic particularities and nutritional status. This approach allowed the establishment of control values, as presented in table 1, without having the pretension that this is the optimal interval for the population health status. Patients with alopecia areata develop vitamin D3 deficiency ( $14.3 \pm 10.7$  ng/mL versus control  $26.8 \pm 14.4$  ng/mL, CI=95%,  $p < 0.05$ ) (table 1, table 6). More than 53.0% of the healthy volunteers included in this study present inadequate levels of 25(OH)D3 (under 30 ng/mL serum). Vitamin D3 deficiency is much more frequent in

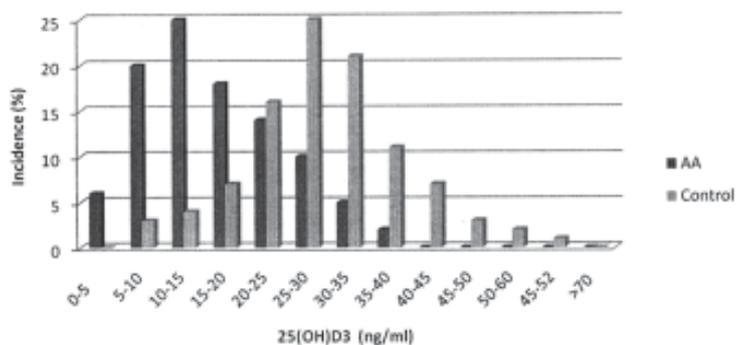


Fig. 5. 25(OH)D3 levels at patients with alopecia areata (AA) and control

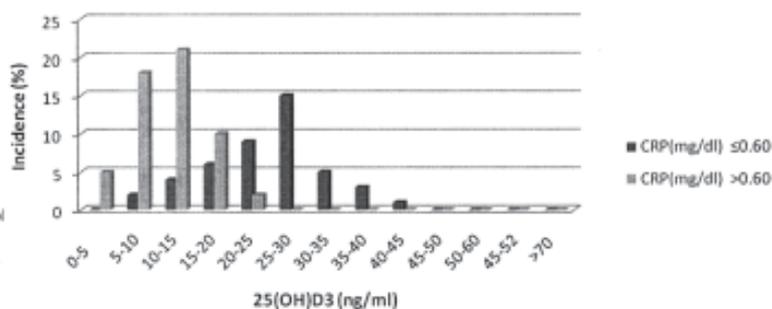


Fig. 6. Status of 25(OH)D3 at patients with alopecia areata for optimal and upper normal levels of CRP.

patients with alopecia areata. Only 6.2% of investigated patients with alopecia areata have an optimal serum value of 25(OH)D3 (30-50ng/mL), and 93.8% have inadequate levels of vitamin D (fig. 5).

25(OH)D3 deficiency is associated with changes of the acute phase proteins. This relation between suboptimal values of 25(OH)D3 and the inflammatory process is statistically supported by the establishment of correlations between serum values of 25(OH)D3 and CRP ( $r = -0.59$ ,  $p < 0.05$ ) (fig. 6), between 25(OH)D3 and ceruloplasmin ( $r = -0.22$ ,  $p > 0.05$ ) (fig. 7), between 25(OH)D3 and albumin ( $r = 0.33$ ,  $p < 0.05$ ) (fig. 8), between 25(OH)D3 and transferrin ( $r = 0.11$ ,  $p > 0.05$ ) (fig. 9). In controls, no statistically significant relationship between these chemical mediators was achieved (table 7).

The results of the study support the previously enunciated idea regarding the participation of vitamin D in the pathogenesis of alopecia areata. Therefore, the authors proved that:

- in patients with alopecia areata significantly lower serum values were obtained for vitamin D as compared to controls (table 1, table 6);

- vitamin D insufficiency (serum levels lower than 30 ng/mL) is much more frequent in patients with alopecia areata (93.8%) versus controls (53.0%).

- suboptimal serum values of vitamin D are associated with a mild inflammatory response in patients with alopecia areata, probably induced by immune stimuli;

Significance	25(OH) D3 (ng/ml)	Alopecia areata(n)	Control (n)
Very severe vitamin D deficiency	1.6 - 5	3	0
Severe vitamin D deficiency	5 – 10	10	2
Vitamin D deficiency	10 – 20	21	9
Suboptimal vitamin D provision	20 – 30	12	35
Optimal vitamin D level	30 – 50	0	38
Upper vitamin D level	50 – 70	0	4
Overdose	>70	0	0

**Table 6**  
COMPARISON OF SERUM 25(OH) D3  
IN ALOPECIA AREATA AND  
CONTROL.

Parameters	Alopecia areata		Control	
	r	p	r	p
25(OH) D3 /CRP	- 0.59	0,00	- 0.09	NS
25(OH) D3/Ceruloplasmin	-0.22	NS	0,00	NS
25(OH)D3/Albumin	0.33	0.03	0.02	NS
25(OH)D3/Transferrin	0.11	NS	0.00	NS

**Table 7**  
STATISTICAL RELATIONSHIP BETWEEN  
SERUM LEVELS OF 25(OH) D3 AND  
ACUTE PHASE RESPONSE MEDIATORS

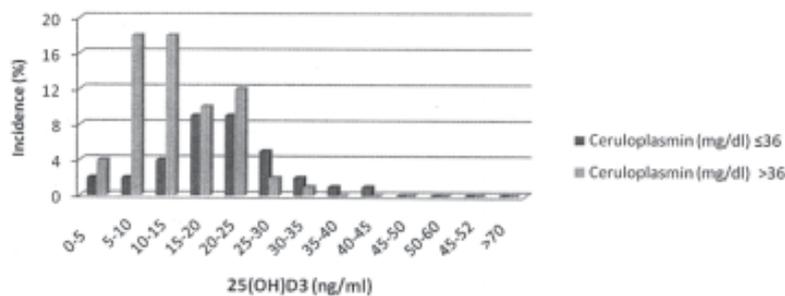


Fig. 7. Status of 25(OH)D3 at patients with alopecia areata for optimal and upper normal levels of ceruloplasmin

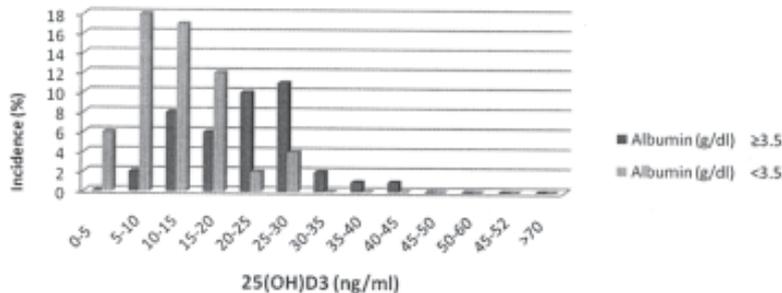


Fig. 8. Status of 25(OH)D3 at patients with alopecia areata for optimal and suboptimal levels of albumin

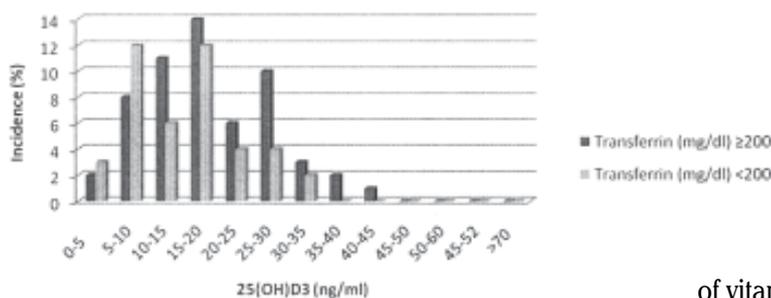


Fig. 9. Status of 25(OH)D3 at patients with alopecia areata for optimal and suboptimal levels of transferrin

- changes in the serum concentrations of positive acute phase proteins (CRP, ceruloplasmin) and negative acute phase proteins (albumin, transferrin) are not representative in patients with alopecia areata with normal levels of vitamin D (30-50 ng/mL) (figs 6, 7, 8 and 9). These findings might be due to the capacity of vitamin D/VDR to stimulate or suppress the genic expression of acute phase proteins and proinflammatory cytokines in the liver. Our results are congruent with those of recent studies, which assert that vitamin D deficiency is reversely correlated with the severity of alopecia areata [19, 20] and could represent a risk factor for this disease [21]. Moreover, the co-existence

of vitamin D and VDR in a tissue regulates the expression of some genes involved in differentiation, proliferation, apoptosis, angiogenesis, inflammation, skin pigmentation, cutaneous adaptive immunity, cutaneous innate immunity, cutaneous antimicrobial effects, hair follicle, cycling, growth regulation of sebaceous gland, photoprotection, wound healing and tissues repair [8,12,13,14,18,19, 20,21].

### Conclusions

The results obtained in this study demonstrate that inadequate levels of vitamin D are more frequently encountered in patients with alopecia areata as compared to controls. Suboptimal levels of vitamin D, detected in

patients with alopecia areata, might constitute a risk factor for this disease. Vitamin D deficiency correction might serve as a prevention approach for the progression of alopecia areata.

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