Topical Calcipotriol versus oral vitamin D in the treatment of alopecia areata

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ABSTRACT

Background: Alopecia areata (AA) is non-scarring hair loss resulting from an autoimmune disorder. Severity varies from patchy hair loss that often spontaneously resolves to severe and chronic cases that can progress to total loss of scalp and body hair.
Aim of the work: To compare the efficacy of topical calcipotriol versus oral vitamin D in alopecia areata.
Patient and Methods: Fifty patients having localized alopecia (<5 patches and <40% scalp involvement) were treated with topical calcipotriol 0.005% twice daily for 3 months (group 1) and oral vitamin D daily for 3 months (group 2). All cases were assessed by grading the degree of improvement of alopecia and dermoscopic evaluation. Estimation of serum levels of 25-hydroxy vitamin D in all patients before the treatment.
Results: There was statistically significant difference with p-value < 0.05 between two study groups regarding to degree of improvement. Dermoscopic findings that explain signs of activity were decreased, and signs of improvement were appeared after 3rd months of treatment. In topical calcipotriol group terminal hair was more than oral vitamin D group, in which signs of activity was still present in some cases.
Conclusion: In conclusion, topical calcipotriol (68% improvement) was better than oral vitamin D in the treatment of mild and moderate alopecia areata. There is no releation between serum vitamin D and efficacy of treatment. However, further studies on larger scales are required to identify the vitamin D receptor deficiency in alopecia areata.

Keywords:
Alopecia areata-Topical calcipotriol-Oral vitamin D.

INTRODUCTION:

Alopecia areata (AA) is a complex genetic, immune mediated disease that targets anagen hair follicles **(Hordinsky, 2013)**. It is a common, nonscarring, autoimmune disease that can affect any hair- bearing area **(Alsantali, 2011)**.

The disease affects children and adults and is characterized by round or oval patches of scalp hair loss, total scalp hair loss (alopecia totalis), universal loss of all hairs (alopecia universalis) **(Hordinsky, 2013)**, or ophiasis pattern which is snake-shaped hair loss around the circumference of the head in the temporal, occipital and frontal areas **(Brzezińska-Wcisło et al., 2014)**.

The treatment of AA may take a long time which is not less than 3 months or more, and in some cases till there is a good and accepted hair regrowth. In most cases there is a need for the combination therapy. Most methods of treatment usually begin with use of one drug with low side effects, then the use of another drug or more, depending on a lot of points. One of those points that considered as the most important one is the severity of the disease **(Galán-Gutiérrez et al., 2009)**.

Vitamin D plays several roles in the body, influencing bone health as well as serum calcium and phosphate levels. Furthermore, vitamin D may modify immune function, cell proliferation, differentiation, and apoptosis **(Dastani et al., 2012)**.
Various immunological cells such as monocytes, T and B lymphocytes and Langerhans cells express both vitamin D receptor and 1α-hydroxylase implicating a vital role of vitamin D in control and regulation of immune mechanisms **(Wadhwa et al., 2015)**. Recently, a connection between some autoimmune diseases and vitamin D deficiency has been reported, and vitamin D deficiency was suggested to act as an environmental trigger for the induction of autoimmunity **(D'Aurizio et al., 2015)**.
Reports have highlighted serum vitamin D deficiency and reduced 1,25-dihydroxyvitamin D(3) receptors (VDR) expression on hair follicles of alopecia areata (AA) patients **(Naranq et al., 2017)**. Deficient serum 25(OH) D levels are present in patients with AA and inversely correlate with disease severity. Accordingly, screening patients with AA for vitamin D deficiencies seems to be of value for the possibility of supplementing these patients with vitamin D **(Çerman, 2015)**.
Calcipotriol is a vitamin D analogue and a potent immunomodulatuary molecule. It may serve as a safe and effective treatment option in mild-to-moderate patchy AA **(Çerman et al., 2015)**.

1. Patients and methods:

It was a prospective cohort, that included 50 patients with localized alopecia areata. Two groups were involved: 25 patients used topical calcipotriol (0.005%) cream twice daily for 3 months }12 (48%) males and 13 (52%) females& their ages ranged from 3 to 35 years, median 7{ as a **group 1**. Their Family history was positive in 12% of patients. One had past history of trauma/ hospitalization. Drug history was negative in 60% of patients, 20% had history of drug intake without improvement, 12% with improvement and 8% with recurrence. None of patients had chronic illnesses or autoimmune disorders and 20% had associated skin disorders, 64% of patients had only one bald patch, 28% had two patches, 4% had three patches and 4% had four patches. The distribution of patches in the scalp ranged from 2% to 7.5%. Majority of patients had the disease for not more than five months with sudden onset in 84% of cases and progressive course in 64% of cases., and 25 patients received oral vitamin D (1 microgram) cap once daily for 3 months }9 (36%) males and 16 (64%) females& their ages ranged from 7 to 40 years, median 9 { as a **group 2**. Their Family history was positive in 20% of patients. One had past history of surgery/hospitalization. Drug history was negative in 72% of patients, 16% had history of drug intake without

improvement, 8% with improvement and 4% with recurrence. None of patients had chronic illnesses or autoimmune disorders and 16% had associated skin disorders. 72% of patients had only one bald patch, 16% had two patches, 8% had three patches and 4% had seven patches. The distribution of patchs in the scalp ranged from 2% to 7%. Majority of patients had the disease for not more than six months with sudden onset in 88% of cases and progressive course in 60% of cases. Patient selection included a written consent. The study plan considering this work was accepted by the Ethical committee of Faculty of Medicine, Fayoum University, for participation in the study. We excluded severe cases as alopecia totalis, universalis and ophiasis, pregnant and lactating women, Contraindications to topical calcipotriol as allergic reactions, hypercalcimia, hypervitaminosis D, severe liver and kidney diseases and contraindication to oral vitamin D intake as sarcoidosis, hyperphosphatemia, hypercalcemia, arteriosclerosis and thrombi, renal stone and renal diseases. All the patients were subjected to detailed history taking, dermatological examination to detect type and severity of alopecia areata (localized or diffuse) and distribution of lesions, dermoscopic examination SCALAR CORPORATION, made in Japan, was intented for confirm the diagnosis and detect activity of alopecia areata, estimation of serum levels of 25-hydroxy vitamin D in all patients before the treatment and a photograph was taken before starting treatment (baseline), during the three months of treatment period& 3 months post stoppage of treatment to detect recurrence.
Follow up was done at monthly intervals for three months and three months post stoppage of treatment, in each visit the patient was asked for compliance, satisfaction and side effects of the treatment.
Response to treatment was be evaluated:

- Subjectively by grading the degree of improvement into 6 degrees: No response (0%), Poor response (0-20%), Some response (20-40%), Good response (40-60%), Very good response (60-90%) and Full regrowth (100%).
- Objectively by patient satisfaction.
- By dermoscopy at each time to evaluate the results as signs of activity and improvement.

RESULTS:

There was no statistically significant difference between topical calcipotriol cream and oral vitamin D regarding degree of improvement of alopecia after 1st month, while there was statistically significant difference between topical calcipotriol cream and oral vitamin D regarding degree of improvement after 2nd and 3rd months ($p > 0.05$) **(table 1& figure 1, 2, 3)**.

Table (1): Comparison between Topical calcipotriol cream and oral vitamin D regarding to degree of improvement of alopecia after first, second and third months of treatment

	Group		Chi square	P value
	Topical calcipotriol cream	oral vitamin D		

Degree of improvement after 1st month:	No response	N	7	6	4.213	0.239 ns
		%	28.0%	24.0%		
	Poor response	N	1	6		
		%	4.0%	24.0%		
	Some response	N	11	8		
		%	44.0%	32.0%		
	Good response	N	6	5		
		%	24.0%	20.0%		
	Very good response	N	0	0		
		%	0%	0%		
	Full regrowth	N	0	0		
		%	0%	0%		
Degree of improvement after 2nd month:	No response	N	7	5	11.908	0.018S
		%	28.0%	20.0%		
	Poor response	N	0	7		
		%	0.0%	28.0%		
	Some response	N	1	0		
		%	4.0%	0.0%		
	Good response	N	5	8		
		%	20.0%	32.0%		
	Very good response	N	12	5		
		%	48.0%	20.0%		
	Full regrowth	N	0	0		
		%	0%	0%		
Degree of	No	N	4	2	10.056	0.040 S

improvement after 3rd month:	response	%	16.0%	8.0%		
	Poor response	N	3	3		
		%	12.0%	12.0%		
	Some response	N	1	7		
		%	4.0%	28.0%		
	Good response	N	0	0		
		%	0%	0%		
	Very good response	N	4	8		
		%	16.0%	32.0%		
	Full regrowth	N	13	5		
		%	52.0%	20.0%		

Ns = non-significant at p value > 0.05, S = Significant at p value < 0.05

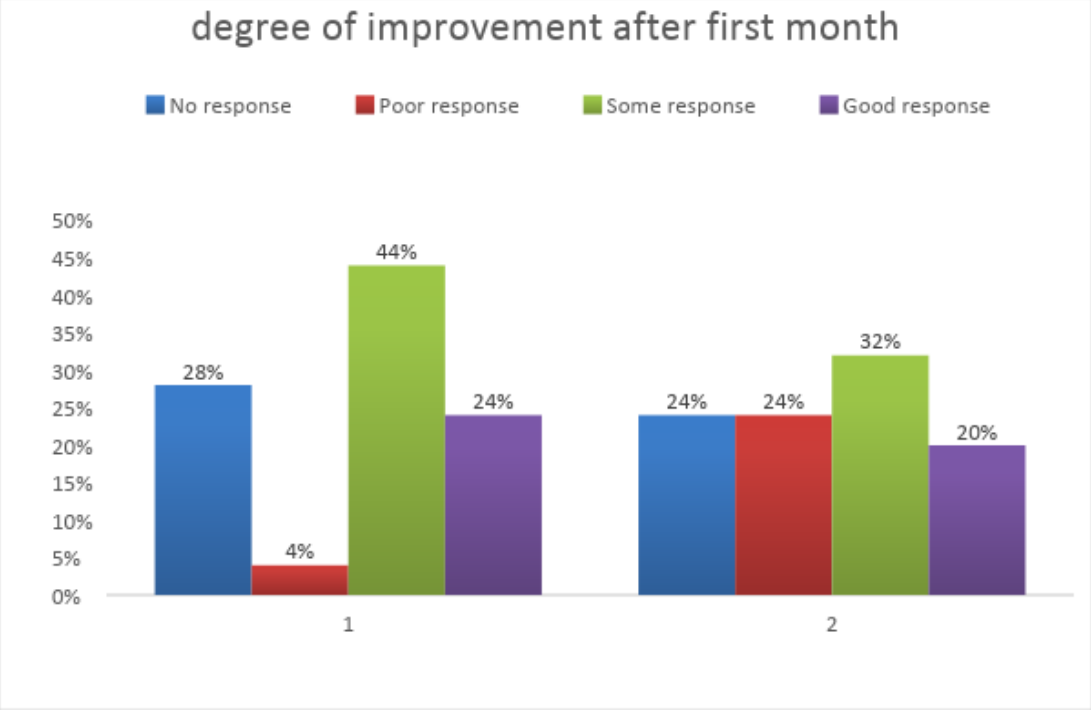

Fig. 1: Comparison between topical calcipotriol 0.005% cream and oral vitamin D regarding the degree of improvement of alopecia after first month of treatment

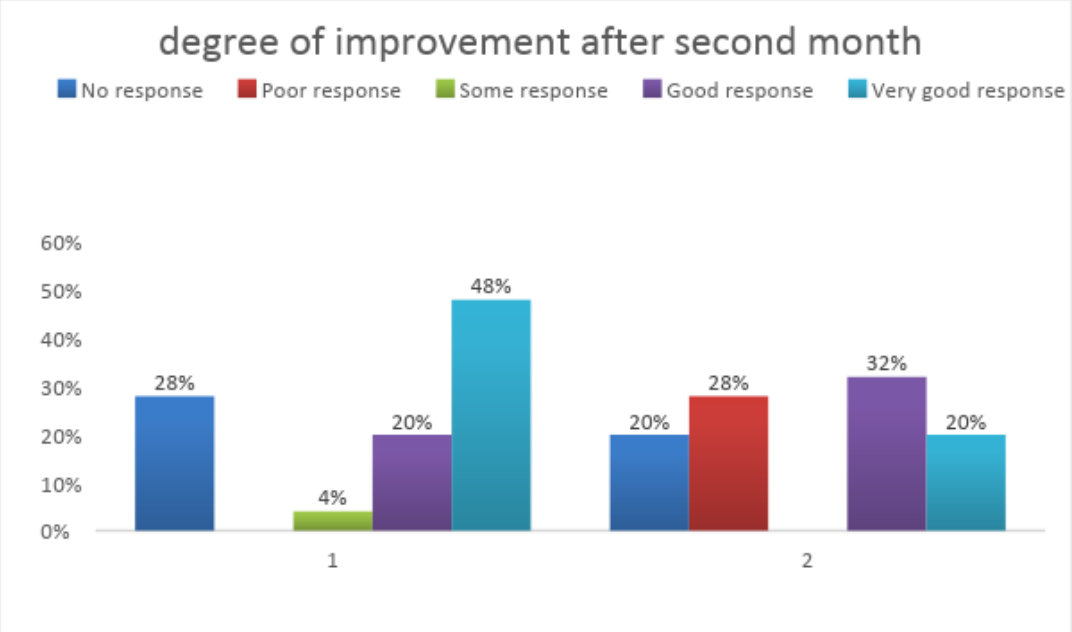

Fig. 2: Comparison between topical calcipotriol 0.005% cream and oral vitamin D regarding the degree of improvement of alopecia after second month of treatment

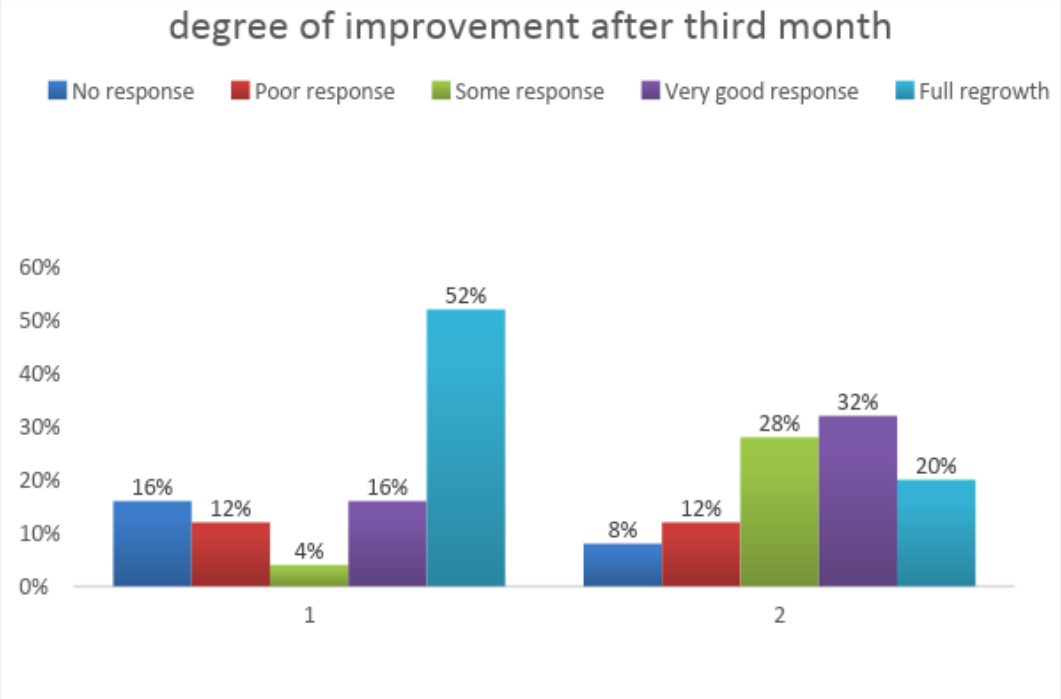

Fig. 3: Comparison between topical calcipotriol 0.005% cream and oral vitamin D regarding degree of improvement of alopecia after third month of treatment

Dermoscopic findings at baseline, after first, second and third months of treatment was shown in **(table 2)**.

Table (2): Demographic data of the included persons regarding dermoscopic findings

		Topical calcipotriol 0.005% cream		Oral vitamin D	
		N	%	N	%
Baseline	Black dots	25	100	25	100
	Yellow dots	19	76	20	80
	Broken hairs	5	20	5	20
	Tapering hairs	11	44	12	48
	Short vellus hair	0	0	0	0
	Terminal hair	0	0	0	0
1st month	Black dots	19	76	20	80
	Yellow dots	19	76	17	68
	Broken hairs	0	0	0	0
	Tapering hairs	0	0	0	0
	Short vellus hair	6	24	5	20
	Terminal hair	0	0	0	0
2nd month	Black dots	7	28	7	28
	Yellow dots	4	25	6	24
	Broken hairs	0	0	0	0
	Tapering hairs	0	0	0	0
	Short vellus hair	6	25	8	32
	Terminal h.	12	48	5	20
3rd month	Black dots	4	16	5	20
	Yellow dots	3	12	4	16
	Broken hairs	0	0	0	0
	Tapering hairs	0	0	2	8
	Short vellus hair	15	60	10	40
	Terminal hair	17	68	13	52

Comparison between patients regarding to measurement of serum vitamin D **(table 3& figure 4)**.

Table (3): Comparison between patients regarding to measurement of serum vitamin D

S. Vitamin D	<30	N	34
		%	68.0%
	>30	N	16
		%	32.0%

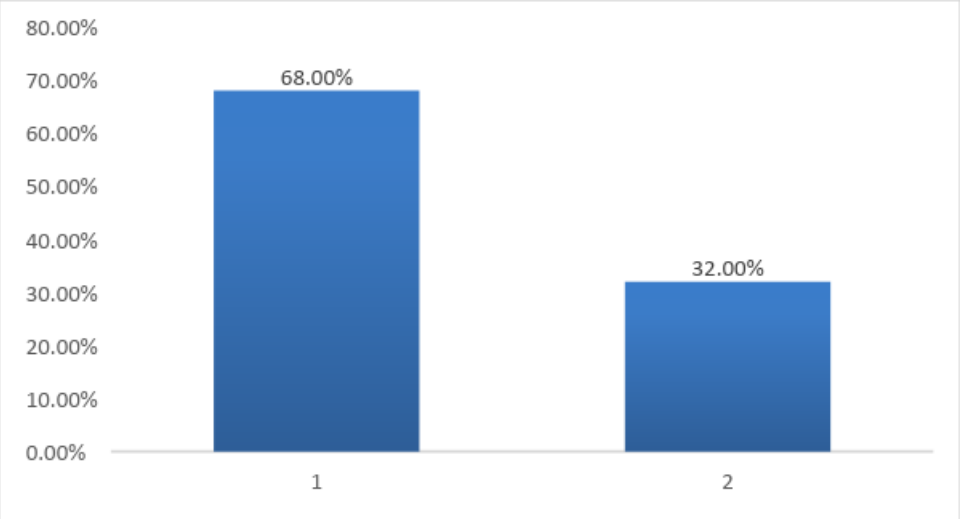

Fig. 4: Comparison between patients regarding to measurement of serum vitamin D

There was no statistically significant difference between degree of improvement of alopecia after third month regarding serum vitamin D in topical calcipotriol cream, serum vitamin D in oral vitamin D ($p > 0.05$) **(table 4& figure 5, 6)**.

Table (3): Comparison between degree of improvement after third month regarding to Serum vitamin D in topical calcipotriol cream, Serum vitamin D in oral vitamin D

		Serum vitamin D in Topical calcipotriol 0.005% cream	Serum vitamin D in oral vitamin D
Degree of improvement after 3 months	No response	24.39±5.59	30.05±1.34
	Poor response	22.48±6.94	28.94±6.47
	Some response	17.03±0.00	27.67±3.49
	Very good response	24.72±5.26	28.35±2.88
	Full regrowth	24.97±6.36	31.58±3.47
F ratio		0.456	0.973
P value		0.767 ns	0.444 ns

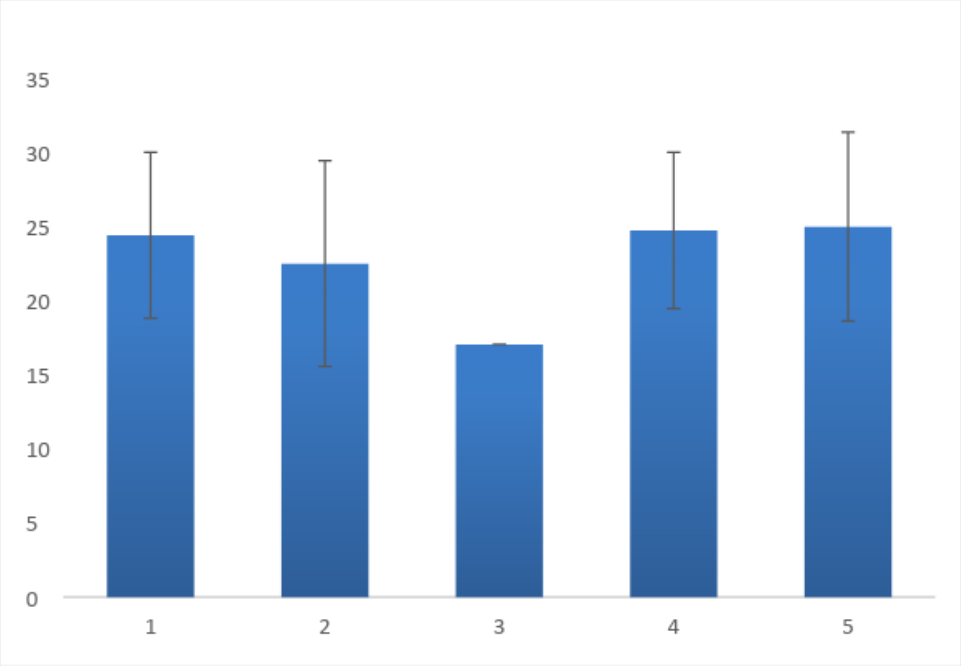

Figure (6): Comparison between degree of improvement after third month regarding to serum vitamin D in topical calcipotriol 0.005% cream group

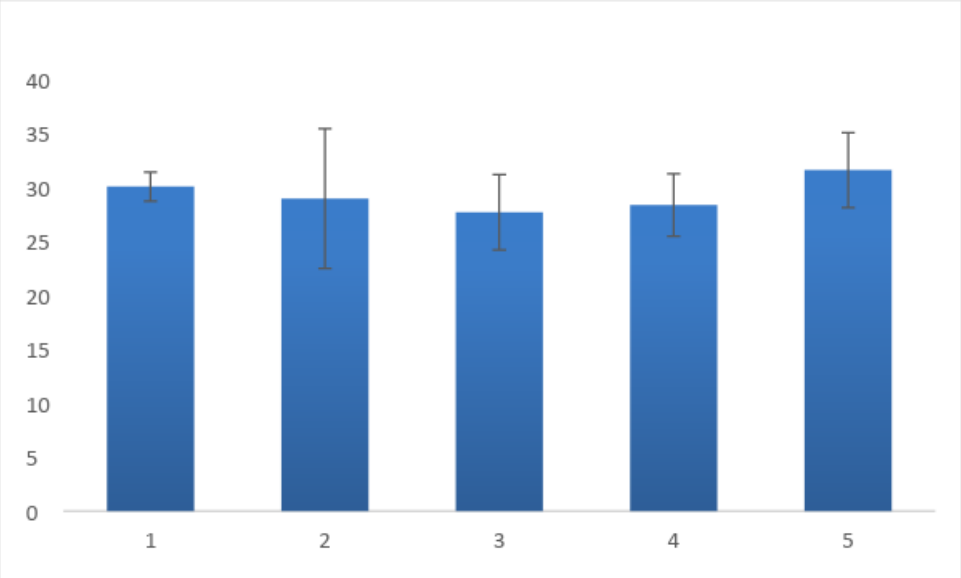

Figure (7): Comparison between degree of improvement after third month regarding to serum vitamin D in oral vitamin D group

DISCUSSION:

After three months of treatment, the first group **(topical calcipotriol)** showed 52% full regrowth, 16% very good response, 4% some response, 12% poor response and 16% no response. The patient satisfaction was 68%.
Baseline dermoscopic findings at the start for diagnosis of alopecia areata showed black dots in 100% of cases, yellow dots in 76%, broken hair in 20% and tapering hairs in 44% of cases. After three months months of treatment, black dots appeared in 4% of cases, yellow dots in 12%, short vellus hair in 60% of cases, terminal hairs in 68%, but broken hair and tapering hairs were disappeared.

After three months of treatment, the second group **(oral vitamin D)** showed 20% full regrowth, 32% very good response, 28% some response, 12% poor response and 8% no response. The patient satisfaction was 52%.

Baseline dermoscopic findings at the start for diagnosis of alopecia areata showed black dots in 100% of cases, yellow dots in 80%, broken hair in 20% and tapering hairs in 48% of cases. After three months months of treatment, black dots appeared in 20% of cases, yellow dots in 16%, short vellus hair in 40% of cases, terminal hairs in 52%, but broken hair were disappeared. Tapering hairs were still present in 8% of cases.
For our knowledge, our study was the first study use oral vitamin D in the treatment of alopecia areata.
Based on the study of **Amor et al** in **2010** who purposed to examine the role of vitamin D in hair growth and the hair cycle; they discussed the possible implications of vitamin D in the clinical care of patients with hair disorders. Initial observations indicate that vitamin D supplementation may be preventive in multiple sclerosis and diabetes mellitus. So an interventional clinical approach could be suggested according to the criteria of EBM (Evidence Based Medecine), also in the light of some our encouraging preliminary results suggest the possible important role of vitamin D not only in the adjuvant therapy but also in decreasing the rate of relapses in these patients and perhaps in preventing the occurrence of the disease **(d'Ovidio et al., 2013)**.
In our study, there was no statistically significant difference between topical calcipotriol cream and oral vitamin D regarding degree of improvement of alopecia after 1st month, while there was statistically significant difference between topical calcipotriol cream and oral vitamin D regarding degree of improvement after 2nd and 3rd months ($p > 0.05$) being better in topical calcipotriol group.
After three months months of treatment dermoscopic findings that explain signs of activity (Black dots, tapering hairs, yellow dots, broken hairs) of the disease were decreased, and signs of improvement (short vellus hairs, terminal hairs) were appeared. In topical calcipotriol group terminal hair was more than oral vitamin D group, in which signs of activity was still present in some cases.
There was no statistically significant difference between topical calcipotriol 0.005% cream and oral vitamin D regarding patient satisfaction and there were no reported side effects of drugs.
All patients of two groups were compliant to treatment and all patients

with positive results had no recurrence after 3 months from stoppage of treatment.

Serum 25(OH)-D levels at 30 ng/ml was the cut-off values for Vitamin D insufficiency **(Elbassiony et al., 2016)**. Serum vitamin D levels were measured at baseline for all patients in our study, 68% of patients had vitamin D insufficiency.

In our study, there was no statistically significant difference between degree of improvement of alopecia in the third month regarding serum vitamin D. The mean serum vitamin D for patients with full regrowth was 26.80±6.38, for pateints with very good response was 27.14±4.00, for pateints with some response was 26.33±4.95, for pateints with poor response was 25.71±6.97and for pateints with no response was 26.28±5.25.
It was meaning that response to treatment has no relation to baseline serum vitamin D, revealing that screening for vitamin D prior to treatment may be not recommended as we found in our study.

CONCLUSION AND RECOMMENDATIONS:

- Topical calcipotriol (68% improvement) was better than oral vitamin D (52%) in the treatment of mild and moderate alopecia areata.
- Topical calcipotriol may be effective in the treatment of mild and moderate patchy (not more than 40% of scalp distribution) alopecia areata.
- There is no relation between serum vitamin D and efficacy of treatment, so it is not recommended to measure vitamin D prior to treatment.
- Oral vitamin D may be a main supplement in treatment of alopecia areata.
- Studies of larger scales are required to identify the vitamin D receptor deficiency in alopecia areata.

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