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Increased prevalence of vitamin D deficiency in patients with alopecia areata: A systematic review and meta-analysis

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Abstract

Background: Alopecia areata (AA) is a hair follicle-specific autoimmune disorder. Vitamin D deficiency has been associated with various autoimmune disorders for its immunomodulatory effects. However, in previous studies, there had been inconsistent association found between AA and vitamin D deficiency.

Objective: To demonstrate the differences of the mean serum 25-hydroxyvitamin D level and prevalence of vitamin D deficiency between AA subjects and non-AA controls.

Methods: A systematic review and meta-analysis of observational studies on AA and serum vitamin D levels and/or prevalence of vitamin D deficiency was performed searching MEDLINE, Cochrane, Web of Science, and Google Scholar databases.

Results: In all, 14 studies including a total of 1,255 AA subjects and 784 non-AA control were analyzed. The mean serum 25-hydroxyvitamin D level was significantly lower in AA subjects (-8.52 ng/dL; 95% confidential interval; -5.50 to -11.53). The subjects with AA had higher odds of vitamin D deficiency of vitamin D deficiency (odds of 3.55; 2.03 to 6.20, mean prevalence of 75.5%; 60.8 to 86.0%). However, it was difficult to find clear correlation between serum 25-hydroxyvitamin D level and extent of hair loss in AA.

Conclusion: The AA subjects had lower serum 25-hydroxyvitamin D level and vitamin D deficiency was highly prevalent compared to non-AA controls. Hence, Vitamin D deficiency should be assessed in AA patients. Furthermore, nutritional supplementation of vitamin D or topical vitamin D analogues can be considered for AA patients with vitamin D deficiency. The limitation of this study is the highly heterogeneity of the included studies.

Key words: Alopecia areata; Vitamin D; Autoimmune; Hair loss; Nutrition; Vitamin

Introduction

Alopecia areata (AA) is a hair follicle-specific autoimmune disorder that causes non-scarring hair loss¹. The prevalence is 0.1–0.2% with the lifetime risk of 2%². As AA is considered a T cell-mediated autoimmune disorder, several studies have shown that patients with AA are more likely to develop other autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, type I diabetes mellitus, and vitiligo compared to the normal population³⁻⁵.

Vitamin D is a group of fat-soluble secosteroids, synthesized in epidermal keratinocytes⁶. As vitamin D from the diet or synthesis in skin is inactive, it is required to be enzymatically converted to its active form, 1,25-dihydroxyvitamin D (1,25(OH)₂D). Among the various roles of vitamin D in the human body, the immunomodulation and its impact on the onset and activity of autoimmune diseases have been discussed⁷. However, there is no mechanism elucidated for the changes in the immunomodulatory function of vitamin D according to its status. Nevertheless, there have been reports of the differences in the risks for onset of various systemic diseases⁸. Particularly, decreased serum vitamin D levels have been reported in patients with several autoimmune disorders⁹⁻¹³.

Recent studies have examined an association of vitamin D deficiency with AA. However, in these studies, the frequency of vitamin D deficiency in subjects with AA was highly heterogenous, and inconsistent associations between vitamin D deficiency and AA were reported. The aim of this systematic review and meta-analysis is to examine the prevalence of vitamin D deficiency in AA patients and their association, comparing serum vitamin D levels and the frequency of vitamin D deficiency in subjects with AA to those in non-AA controls.

Materials and Methods

This study follows the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) principles¹⁴ (Fig. 1).

Search strategy

We conducted a comprehensive search to identify all relevant studies regardless of language, publication status, and year of publication. Two main reviewers (S.L. and B.K) searched MEDLINE, Cochrane Reviews, Web of Science, and Google Scholar databases using the search term ((“areata”) AND ((“vitamin D”) OR (“25-hydroxyvitamin D”) OR (“1,25-dihydroxyvitamin D”))) for literature published from January 1, 1946 to October 20, 2017. We confined the search scope to the title of article for the Google Scholar search because of the excessive amount of nonspecific data retrieved.

Since the number of total available articles was not expected to be large, a reference list of the publications retrieved was also screened manually to obtain additional available sources. A total of 67 articles were selected for initial screening excluding duplicated items.

Study selection

Two main reviewers independently evaluated the titles and abstracts of the retrieved literature. In cases of discrepancy between the two main reviewers, a final decision was made by consensus discussion with the other two reviewers (C.L and W.L). Studies were selected based on the following inclusion criteria: (1) human study relevant to AA, (2) participants of all age groups with a diagnosis of AA, (3) observational study with a comparable non-AA control group, and (4) either data for the serum vitamin D level or frequency of vitamin D deficiency given for each group. Exclusion criteria consisted of (1) animal or experimental (both *in vivo* and *in vitro*) studies, (2) interventional studies, (3) no control group for comparison, (4) conference proceedings, and (5) case reports or case series. If

the abstract did not provide enough information to include or exclude the study, a full-text evaluation was performed to determine eligibility. Finally, 14 studies were included in the pooled analysis (Fig. 1).

Data extraction and quality assessment

The reviewers compiled the data in a predefined spreadsheet, performing data extraction and quality assessment for the studies included. The extracted data from each study were study year, study setting (country and period), study design, and control setting. The number of subjects and controls, the proportion of males, and the mean age were also collected. The main outcome for assessment was serum level of 25-hydroxyvitamin D (25(OH)D), the major circulating form of vitamin D, and prevalence of vitamin D deficiency in the AA subjects and non-AA controls. Additionally, if there was an assessment of changes in serum 25(OH)D level according to the severity of AA in each study, it was also included in the analysis. The Newcastle-Ottawa scale¹⁵ was used for quality assessment to evaluate the potential risk of bias for the included studies.

Data synthesis and outcome

Pooled analyses were performed both for serum 25(OH)D levels (continuous data) and the prevalence of vitamin D deficiency (categorical data). The heterogeneity of the included studies was calculated using the chi-squared test for heterogeneity (with $p < 0.1$ indicating statistical significance) and the I^2 statistic for inconsistency. We expected a significant degree of heterogeneity of the included studies because vitamin D synthesis and serum levels can be affected by numerous factors⁶ such as the study setting (e.g. latitude, season, amount of sunshine), ethnic differences (e.g. skin color, amount of hair), age, sex, lifestyle, and others. Therefore, a random-effects model was used for the synthesis of data. The results were expressed using a forest plot. The publication bias was evaluated through visual inspection of a funnel plot and Egger's test. The Fail-safe N by Rosenthal was utilized for sensitivity

analysis. For statistical analysis, R version 3.2.0 software (R Foundation for Statistical Computing, Vienna, Austria) was used. A p-value less than 0.05 was considered statistically significant.

Results

Study characteristics

The characteristics of the 14 included studies are summarized in Table 1. All consisted of case-control studies reporting at least either serum 25(OH)D level or frequency of vitamin D deficiency in subjects with AA compared to non-AA controls. They were judged to have moderate quality in the setting of case and control analysis and the manner of exposure ascertainment on the quality assessment (Fig. 2). As expected, the setting of studies varied widely, with the location of countries varying from tropical to temperate, and seasonally deviant. In addition, there was no strict control for skin color or ethnicity of the study population in most studies. A total of 1255 AA subjects and 784 non-AA controls were included in the analysis.

Serum 25-hydroxyvitamin D levels and alopecia areata

Eleven of the 14 studies provided data on serum 25(OH)D levels for each group (Table 2). The pooled mean difference was calculated by combining the data sets from the above studies (Fig. 3A). In the random effects model, the mean serum 25(OH)D level in the AA group was lower than that in the non-AA control group by 8.52 ng/dL (95% confidential interval (CI); -11.53 to -5.50 ng/dL). The heterogeneity of the studies was estimated to be high ($I^2=84%$, $p<0.01$). The study by Unal and Gonulalan¹⁶ was thought to be an important contributor to this heterogeneity, because its study population was composed of pediatric patients with AA. When pooling the remaining 10 studies of adult AA patients, the heterogeneity was slightly lower compared to the original analysis ($I^2=74%$), and a consistent outcome was given with the mean difference of 9.52 ng/dL (95% CI; -10.57 to -8.46

ng/dL). The remainder of the heterogeneity was believed to originate from the variable settings of the study environments. In the subgroup analysis for country and season of the study setting, the heterogeneity was further reduced, but its statistical validity could not be judged to be better than the crude analysis because of the small number of pooled studies. The funnel plot for the meta-analysis showed moderate symmetry (Fig. 4A). In Egger's test for funnel plot asymmetry, the risk of publication bias was estimated to be low ($p=0.76$). As the safety factor by Rosenthal's fail-safe N was 600, the effect of sample size on this meta-analysis was judged to be stable.

Vitamin D deficiency and alopecia areata

Ten of the 14 studies provided data on the frequency of vitamin D deficiency in each group (Table 2). A diagnosis of vitamin D deficiency was made when the serum 25(OH)D level was lower than 20 or 30 ng/dL depending on the study. The pooled OR was calculated by combining the data set using an inverse variance method (Fig. 3B). In the random effects model, the subjects with AA had odds of 3.55 (95% CI; 2.03 to 6.20) of having vitamin D deficiency. Its mean prevalence among AA patients was 75.5% (95% CI; 60.8 to 86.0%). The heterogeneity of the studies was high ($I^2=71%$, $p<0.01$).

Similarly, in the subgroup analysis stratified according to variables related to the study setting (country and season of the study), the overall heterogeneity was reduced. Nevertheless, its statistical validity was not superior to the crude analysis because of the small number of pooled studies. A moderate symmetry was observed in the funnel plot (Fig. 4B). The risk of publication bias was evaluated to be low in Egger's test ($p=0.90$). The size of the effect was calculated to be relatively stable with the Rosenthal's fail-safe N of 237.

Correlation of serum 25-hydroxyvitamin D levels with severity of alopecia areata

For nine of the 14 studies, the association between serum 25(OH)D levels and severity of AA was analyzed. Three of the nine studied yielded a linear regression between the Severity of Alopecia Tool

(SALT) score¹⁷ and serum 25(OH)D levels. On the other hand, for the remaining six studies, the differences in serum 25(OH)D level were analyzed according to severity of AA (mild, moderate, and severe defined by each study's own criteria). As a result, in four of the nine studies, there were negative associations found between serum 25(OH)D levels and severity of AA. In contrast, the other five studies did not show any association between them. The pooling of data was not possible as the variables and modalities of statistical analyses were too diverse among the studies. In addition, the possibility of publication bias could not be ruled out in remaining five of the 14 studies without reporting an association between serum 25(OH)D level and severity of AA.

Discussion

This systematic review and meta-analysis was conducted to clarify the association between AA and vitamin D deficiency, which has been consistently raised in recent studies. Pooled data for serum 25(OH)D levels revealed that subjects with AA had lower serum levels by 8.52 ng/dL than non-AA controls. However, this interpretation could not be applied universally to children because the only report studied for pediatric AA patients¹⁶ yielded no difference between the two groups. Meanwhile, vitamin D deficiency was found in 609 of the 1133 subjects in the AA group and in 200 of the 658 subjects in the control group, with a pooled OR of 3.55. This result suggests the close association between AA and vitamin D deficiency, despite the conflicting results reported in previous studies^{16,18-30}. Vitamin D deficiency is closely associated with increased susceptibility to infection, fatigue, bone loss, and mood instability. Therefore, physicians should assess serum 25(OH)D levels to screen for potential vitamin D deficiency in patients with AA, considering its high prevalence in AA patients. However, it was difficult to conclude whether there is a definite correlation between serum 25(OH)D levels and the severity of AA (extent of hair loss). There have been several reports on the association between vitamin D deficiency and different autoimmune disorders, including AA⁹⁻¹³. Moreover, patients with AA have been found to be more prone to other autoimmune and inflammatory diseases

compared to the normal population³⁻⁵. From the results of this review, we can expect there is a crucial role for vitamin D in AA, like in other autoimmune diseases.

The active form of vitamin D, 1,25(OH)₂D, has modulatory effects on the innate and adaptive immune system⁶. Vitamin D inhibits the formation of dendritic cells and reduces T cell activation. In addition, vitamin D has been reported to be involved not only in inhibiting Th1 differentiation, but also in developing tolerance to auto-antigens, increasing CD4+ CD25+ regulatory T cell activity. The beneficial effects of topical vitamin D analogues in psoriasis have been extensively studied³¹, and some positive outcomes have been reported with oral supplementation of vitamin D³². Moreover, the preventive effect of vitamin D supplementation for various autoimmune diseases were noted in a systematic review³³. To date, the causality has not been elucidated whether AA itself induces vitamin D deficiency through a negative effect on vitamin D synthesis, or whether vitamin D deficiency serves as an etiologic factor in the development of AA. However, the association found in this study can be a theoretical background for the nutritional supplementation of vitamin D, and application of topical vitamin D analogues for AA patients with vitamin D deficiency or resistant to conventional treatments. Moreover, there have been some reports describing beneficial effects of vitamin D on hair regrowth in AA³⁴⁻³⁶. Nevertheless, because there have been no well-designed interventional studies on the effects of vitamin D or its analogues for AA, further research is needed to evaluate their potential therapeutic application.

A major limitation of this study is that the study population and settings of the included studies were highly heterogeneous. Because serum 25(OH)D levels can be influenced by various factors including geographic features, season, ethnicity, skin color, and lifestyle, care should be taken when interpreting results unifying these conditions. In addition, all the studies included had a cross-sectional nature, and therefore did not show any time-series relationships and casualty between the severity and course of the disease and serum 25(OH)D levels.

Conclusion

In our study, patients with AA had lower serum 25(OH)D levels by 8.52 ng/dL and the odds of vitamin D deficiency was 3.55 compared to the non-AA population, with the mean prevalence of 75.5%. Physicians are advised to screen for potential vitamin D deficiency in patients with AA. In terms of therapeutic application, physicians can consider oral supplementation of vitamin D or applying topical vitamin D analogues for AA patients with vitamin D deficiency or resistance to conventional treatments. However, a well-designed interventional study is needed to examine the beneficial effects of vitamin D supplementation on hair regrowth in AA patients.

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Figures

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

flowchart of literature search

AA. Alopecia areata.

Figure 2. Quality-assessment of the included studies using Newcastle-Ottawa scale

Figure 3. Forest plots of the meta-analyses

(A) Serum 25(OH)D level.

(B) Vitamin D deficiency.

SD, standard deviation; MD, mean difference; CI, confidential interval; OR, odds ratio;

Vit D Def, Vitamin D deficiency; 25(OH)D, 25-hydroxyvitamin D.

Figure 4. Funnel plots of the meta-analyses

(A) Serum 25(OH)D level.

(B) Vitamin D deficiency.

25(OH)D, 25-hydroxyvitamin D.

Tables

Table 1. Characteristics of the included studies

Study	Study setting	Study design	Control setting	No. of subjects		Age, mean (SD), y		Male, n (%)	
				AA	Control	AA	Control	AA	Control
Erpolat et al. (2017) ¹⁸	Turkey October 2010 to March 2011	Case-control	Not specified	41	32	32.8 (7.5)	32.7 (7.5)	26 (63.4%)	18 (56.3%)
Conic et al. (2017) ¹⁹	US Alopecia registry from 2005 to 2014	Case-control	Patients with diagnosis of seborrheic dermatitis without any concomitant hair loss	58	172	33.54 (19.28)	35.80 (15.56)	184 (31.5%)	46 (26.7%)
Unal and Gonulalan (2017) ¹⁶	Turkey November 2015 to March 2016	Case-control	Individuals who visited to the outpatient clinic and aged under 18	20	34	Male 12.4 (4.2)	Male 16.6 (0.8)	14 (70.0%)	15 (44.2%)
Ghafoor and Anwar	Pakistan October 2014 to	Case-control	Age- and sex-matched healthy	30	30	23.77 (8.6)	24.03 (8.62)	12 (40.0%)	12 (40.0%)

Study	Study setting	Study design	Control setting	No. of subjects		Age, mean (SD), y		Male, n (%)	
				AA	Control	AA	Control	AA	Control
(2017) ²⁰	March 2015		controls						
Bhat et al. (2017) ²⁹	India May 2015 to October 2015	Case-control	Age- and sex-matched healthy controls	50	35	22.4 (8.6)	29.2 (7.6)	NR (NR)	NR (NR)
Attawa et al. (2016) ²¹	Egypt April 2014 to November 2014	Case-control	Healthy individuals	23	23	26.44 (10.87)	29.39 (8.10)	15 (65.2%)	14 (60.9%)
Darwish et al. (2016) ²²	Egypt Study period not specified	Case-control	Age- and sex-matched healthy controls	30	20	28.67 (10)	24.8 (6)	13 (43.3%)	10 (50.0%)
Bakry et al. (2016) ²³	Egypt October 2013 to March 2014	Case-control	Age-, sex-, body mass index-matched healthy controls	60	60	20.70 (10.85)	23.71 (7.45)	36 (60.0%)	28 (46.7%)

Study	Study setting	Study design	Control setting	No. of subjects		Age, mean (SD), y		Male, n (%)	
				AA	Control	AA	Control	AA	Control
Ogrum et al. (2015) ²⁴	Turkey March 2011 to May 2011	Case-control	Age-, sex- and skin phototype-matched healthy controls	40	40	31.23 (7.34)	30.58 (7.19)	21 (52.5%)	21 (52.5%)
Mahamid et al. (2014) ³⁰	Israel March 2010 to May 2011	Case-control	Individuals with no history of alopecia areata from same out-patient population	23	20	24.2 (12.3)	27.0 (11.3)	14 (60.9%)	13 (65.0%)
Cerman et al. (2014) ²⁵	Turkey November 2012 to March 2013	Case-control	Age- and sex-matched volunteers from hospital staff	86	58	32.21 (9.60)	32.55 (9.78)	56 (65.1%)	34 (58.6%)
d'Ovidio et al. (2013) ²⁶	Italy October 2010 to March	Case-control	Healthy individuals	15 6	148	32.8 (NR)	34.5 (NR)	45 (28.9%)	18 (12.2%)

Study	Study setting	Study design	Control setting	No. of subjects		Age, mean (SD), y		Male, n (%)	
				AA	Control	AA	Control	AA	Control
2012									
El-Mongy et al. (2013) ²⁷	Egypt January 2011 to June 2011	Case-control	Healthy individuals	70	70	27.79 (9.12)	30.49 (11.06)	37 (52.9%)	44 (62.9%)
Yilmaz et al. (2012) ²⁸	Turkey June 2010 to September 2010	Case-control	Healthy individuals	42	42	30.8 (8.2)	29.3 (7.4)	28 (66.7%)	29 (69.1%)

SD, standard deviation; AA, alopecia areata; NR, not reported.

Table 2. Outcomes of the included studies

Study	No. of subjects		Serum 25(OH)D level, mean (SD), ng/dL		Vitamin D deficiency, n (%)		Correlation between serum 25(OH)D levels and severity of AA
	AA	Control	AA	Control	AA	Control	
Erpolat et al. (2017) ¹⁸	41	32	9.8 (25.85)	8.1 (24.89)	40 (97.6%)	31 (96.9%)	NR
Conic et al. (2017) ¹⁹	584	172	NR (NR)	NR (NR)	228 (39.0%)	21 (12.2%)	NR
Unal and Gonulalan (2017) ¹⁶	20	34	15.47 (7.66)	11.09 (10.53)	NR (NR)	NR (NR)	Negative linear correlation between serum vitamin D level and SALT score (r=-.831, p<0.001)
Ghafoor and Anwar (2017) ²⁰	30	30	13.5 (13.78)	22.5 (12.04)	NR (NR)	NR (NR)	NR

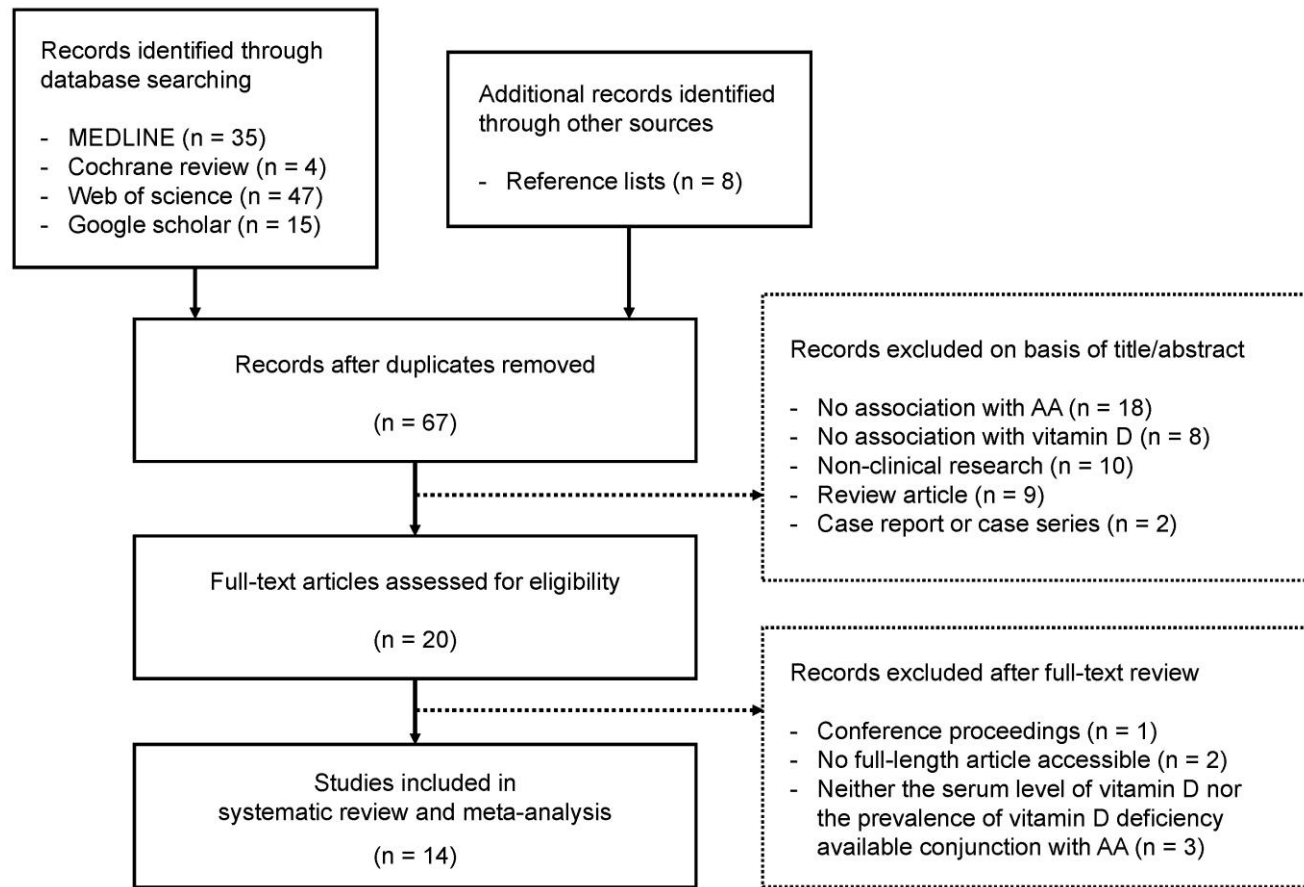
Study	No. of subjects		Serum 25(OH)D level, mean (SD), ng/dL		Vitamin D deficiency, n (%)		Correlation between serum 25(OH)D levels and severity of AA
	AA	Control	AA	Control	AA	Control	
Bhat et al. (2017) ²⁹	50	35	16.6 (5.9)	25.49 (1.02)	21 (42.0%)	10 (28.6%)	Negative linear correlation between serum vitamin D level and SALT score (r=-.730, p<0.001) S1 19.02 (4.40) n=38 S2 9.00 (2.80) n=12
Attawa et al. (2016) ²¹	23	23	14.13 (8.72)	22.43 (10.94)	21 (91.3%)	21 (91.3%)	No difference in the frequency of vitamin D deficiency found according to the severity of AA

Study	No. of subjects		Serum 25(OH)D level, mean (SD), ng/dL		Vitamin D deficiency, n (%)		Correlation between serum 25(OH)D levels and severity of AA
	AA	Control	AA	Control	AA	Control	
Darwish et al. (2016) ²²	30	20	7.52 (6.24)	31.7 (12.29)	NR (NR)	NR (NR)	No correlation between serum vitamin D level and SALT score
Bakry et al. (2016) ²³	60	60	17.64 (6.25)	26.47 (7.00)	50 (83.3%)	14 (23.3%)	Negative relation shown according to the severity of AA (mild/moderate/severe)
Ogrum et al.	40	40	NR (NR)	NR (NR)	39 (97.5%)	39 (97.5%)	NR

Study	No. of subjects		Serum 25(OH)D level, mean (SD), ng/dL		Vitamin D deficiency, n (%)		Correlation between serum 25(OH)D levels and severity of AA
	AA	Control	AA	Control	AA	Control	
(2015) ²⁴							
Mahamid et al. (2014) ³⁰	23	20	11.32 (10.18)	21.55 (13.62)	16 (69.6%)	5 (25.0%)	NR
Cerman et al. (2014) ²⁵	86	58	11.84 (6.18)	23.57 (9.03)	78 (90.7%)	31 (53.4%)	Negative linear correlation between serum vitamin D level and SALT score (r = -409, p <0.001)
							S1 12.57 (6.32) n=41

Study	No. of subjects		Serum 25(OH)D level, mean (SD), ng/dL		Vitamin D deficiency, n (%)		Correlation between serum 25(OH)D levels and severity of AA
	AA	Control	AA	Control	AA	Control	
							S2 8.41 (4.11) n=15
d'Ovidio et al. (2013) ²⁶	156	148	NR (NR)	NR (NR)	66 (42.3%)	44 (29.7%)	No correlation between serum vitamin D level and the disease severity
El-Mongy et al. (2013) ²⁷	70	70	26.6 (13.06)	33.73 (22.4)	50 (71.4%)	36 (51.4%)	No correlation between serum vitamin D level and the disease severity
Yilmaz et al. (2012) ²⁸	42	42	13.38 (7.09)	20.51 (8.45)	NR (NR)	NR (NR)	No correlation between serum vitamin D level and the disease severity

25(OH)D, 25-hydroxyvitamin D; SD, standard deviation; AA, alopecia areata; NR, not reported.



	Case definition	Case representativeness	Control selection	Control definition	Age- and sex- matching	Additional matching	Ascertainment of exposure	Same method for case and control	Non-response rate	Total
Erpolat et al. (2017)	●	●	●	●	●	●	●	●	●	6
Conic et al. (2017)	●	●	●	●	●	●	●	●	●	4
Unal and Gonulalan (2017)	●	●	●	●	●	●	●	●	●	6
Ghafoor and Anwar (2017)	●	●	●	●	●	●	●	●	●	6
Bhat et al. (2017)	●	●	●	●	●	●	●	●	●	6
Attawa et al. (2016)	●	●	●	●	●	●	●	●	●	6
Darwish et al. (2016)	●	●	●	●	●	●	●	●	●	6
Bakry et al. (2016)	●	●	●	●	●	●	●	●	●	8
Ogrum et al. (2015)	●	●	●	●	●	●	●	●	●	6
Mahamid et al. (2014)	●	●	●	●	●	●	●	●	●	6
Cerman et al. (2014)	●	●	●	●	●	●	●	●	●	8
d'Ovidio et al. (2013)	●	●	●	●	●	●	●	●	●	5
El-Mongy et al. (2013)	●	●	●	●	●	●	●	●	●	6
Yilmaz et al. (2012)	●	●	●	●	●	●	●	●	●	6

