Exploring the Relationship Between Alopecia Areata, Vitamin D and Calcium Levels: Ameta-Analysis and Analytical Review

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Abstract
Background: The purpose of this study is to investigate any possible relationships between serum calcium and vitamin D levels and alopecia Areata (AA). **Study design:** A Meta-analysis and analytical review. **Place and Duration** This study was conducted in Sudan-Khartoum (Khartoum Teaching Hospital) Sudan from January 2019 to January 2020. **Methodology:** Key focal points of this study included evaluating serum vitamin D levels and the prevalence of vitamin D deficiency, alongside the secondary assessment of serum calcium levels. The chosen studies were subjected to statistical analysis that included odds ratio (OR) and standardized mean difference (SMD) with 95% confidence intervals (CI). **Results:** Data from eight case-control studies and two cross-sectional studies are included in this meta-analysis. A meta-analysis using a random-effects model revealed that those with AA were more likely to have vitamin D deficiency ($p < 0.001$) and had considerably lower serum vitamin D levels ($p < 0.001$). Serum calcium levels, however, showed no discernible variation ($p = 0.143$). Subgroup analysis revealed that while research design, matched control, and study country may have an impact on vitamin D insufficiency heterogeneity, characteristics including mean age, country, and matched control may have an impact on serum vitamin D levels. **Conclusion:** Rather than low calcium levels, patients with AA have deficiencies in their serum vitamin D levels. Vitamin D deficiency screening and therapy may be beneficial in the treatment of people with AA.
Keywords: **Vitamin D Deficiency, Serum Calcium, Meta-Analysis, Alopecia Areata.**

Introduction

An autoimmune condition called alopecia areata (AA) causes non-scarring hair loss, affecting about 2% of people globally. [1]. The etiology of AA is multifactorial, involving genetic predisposition, environmental triggers, and immune dysregulation [2]. While the precise mechanisms underlying AA pathogenesis remain elusive, emerging evidence suggests a potential role for micronutrient deficiencies, particularly in vitamin D and calcium.

It is commonly recognized that vitamin D, a steroid hormone mostly generated in the skin when exposed to sunlight, has immunomodulatory properties [3]. Numerous studies have connected vitamin D inadequacy to autoimmune disorders such as multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus. [4]. Recent research has also examined the connection between vitamin D status and AA; it has been shown in several studies that AA patients have lower serum vitamin D levels than healthy controls [5, 6].

Calcium, an essential mineral involved in various cellular processes, including hair follicle cycling, has also been implicated in AA pathogenesis. Calcium signaling has a significant role in regulating hair follicle development and cycling, and alterations in calcium homeostasis have been observed in hair loss disorders [7]. However, the relationship between serum calcium levels and AA remains less clear, with conflicting findings reported in the literature [8, 9].

Given the potential significance of calcium and vitamin D in the pathogenesis of AA, a comprehensive review and meta-analysis are required to elucidate their functions. The goal of this study is to fully evaluate the connections between blood levels of calcium and vitamin D and AA, providing information about potential management implications for AA.

This introduction outlines the growing body of evidence suggesting a link between AA and micronutrient deficiencies, particularly in vitamin D and calcium. By synthesizing existing literature and conducting a meta-analysis, this study seeks to contribute to our understanding of the pathophysiology of AA and inform strategies for its clinical management.

Methodology

The analysis was done according to PRISMA strategy. After first screening abstracts, we chose pertinent full-text publications and then manually looked through reference lists to find other pertinent papers, differentiation (WMD); and (6) disseminated in peer-reviewed literature. The following were the exclusion criteria: (a) research without a defined control group; (b) the existence of additional conditions that affect calcium levels and 25-hydroxyvitamin D levels; (c) reviews, case studies, and abstracts; and (d) research published in a language except English.

Serum vitamin D levels and its deficiency were the major outcomes, whereas serum calcium levels were the secondary objective. Depending on the study's criteria, a serum 25(OH)D level below 20 or 30 ng/dL was considered vitamin D deficiency.

doi.org/10.31838/hiv24.01.2 Received: 13.11.23, Revised: 17.12.23, Accepted: 14.01.24.

By comparing AA patients to healthy controls, the odds ratios for vitamin D deficiency were determined. If heterogeneity existed, pooling was done using the DerSimonian and Laird technique; if not, a model of fixed effect was used.

We computed and aggregated mean differences in serum 25-hydroxyvitamin D and calcium levels using weighted mean difference. It was evaluated by I2 and Q statistics. Sensitivity analysis was carried out by eliminating each study one at a time, and publication bias was assessed. Subgroup analysis looked at the predefined components' extra impacts. At $p < 0.05$, statistical significance was established. Software known as STATA MP 14.0 was used for analysis.

Results

There are 10 studies that were eligible to conduct the meta-analysis. The range of the patients in these articles was between 40 to 700 patients. The studies considered were from different countries including Pakistan, Turkey, Nepal and Egypt.

Data on the individuals' serum levels of vitamin D, vitamin D deficiency, and calcium deficiency were obtained from the investigations. Significant inter-study heterogeneity ($I2 > 50\%$) was noted during the pooled meta-analysis for the following: serum calcium level ($p < 0.001$), vitamin D deficiency ($I2 = 81.10\%$, $p < 0.001$), and vitamin D level ($I2 = 87.90\%$, $p < 0.001$). For these studies, a model of random effect was used. The meta-analysis of blood vitamin D levels and vitamin D deficiency showed no evidence of publication bias. Funnel plots showed that there was no evidence of publication bias for blood vitamin D levels or vitamin D deficiency.

Consequently, these results suggest that the meta-analysis was not influenced by publication bias, affirming the statistical robustness of the findings.

The pooled analysis for serum calcium, vitamin D and, vitamin D deficiency was carried out using the random-effects model based on the Q test and I2 test suggesting inter-study heterogeneity. The findings of the ten studies that examined blood vitamin D levels revealed that individuals with AA had significantly lower mean serum vitamin D levels than controls.

The reliability of the findings was evaluated by a sensitivity analysis. Even after methodically eliminating every case-control study, the stability of the current meta-analysis was demonstrated by the consistent results for the meta-analysis of vitamin D insufficiency and level.

The comparison is displayed in Table 1.

Table 1: Comparison of Data from Studies Included.

Study	Study Design	Male %Age		Age (In Years)		Sample Size			Country	Outcomes
		Control	AA	Control	AA	Total	Control	AA		
Marahatta S, 2019 [10]	Case-control study	15 (48.4%)	16 (51.6%)	30.50 ± 9.032	28.37± 10.070	60	30	30	Nepal	Vitamin D level, Deficiency
Rehman F, 2019 [11]	Case-control study	91 (67.41%)	91 (67.41%)	26 ± 13.20	26 ± 12.89	270	135	135	India	Vitamin D level, deficiency, calcium level
Siddappa H, 2019 [12]	Case-control study	58 (58%)	72 (72%)	28.96±11.49	24.52 ± 10.06	200	100	100	India	Vitamin D level, deficiency
Ghafoor R, 2017 [13]	Case-control study	12 (40%)	12 (40%)	24.03 ± 8.62	23.77 ± 8.86	60	30	30	Pakistan	Vitamin D level
Erpolat S, 2017 [14]	Case-control study	18 (56.3%)	26 (63.4%)	32.7 ± 7.5	32.8 ± 7.5	73	32	41	Turkey	Vitamin D level, deficiency, calcium level
Darwish NMM, 2017 [15]	Case-control study	10 (50%)	13 (43.3%)	24.8 ± 6	28.67 ± 10	50	20	30	Egypt	Vitamin D level, calcium level
Bakry O.A., 2016 [16]	Case-control study	28 (46.7%)	36 (60%)	23.71 ± 7.45	20.7 ± 10.85	120	60	60	Egypt	Vitamin D level, deficiency
Fattah N.S.A.A., 2015 [17]	Case-control study	18 (60%)	18 (60%)	25.1 ± 6.9	26.8 ± 6.9	60	30	30	Egypt	Vitamin D level, deficiency
Attawa E, 2016 [18]	Cross-sectional study	14 (60.9%)	15 (65.2%)	29.39 ± 8.10	26.44 ± 10.87	46	23	23	Egypt	Vitamin D level, deficiency
Aksu Cerman A, 2014 [19]	Cross-sectional study	34 (29.1%)	56 (47.9%)	32.55 ± 9.78	32.21 ± 9.60	144	58	86	Turkey	Vitamin D level, Vitamin D deficiency

Discussion

This meta-analysis systematically evaluated the relationship between alopecia areata (AA) and serum levels of vitamin D and calcium. Our comprehensive analysis included data from 10 studies, which enabled us to draw robust conclusions regarding the association between AA and these essential nutrients.

Our research showed a strong correlation between AA and decreased serum vitamin D levels as well as a higher risk of vitamin D deficiency in AA patients relative to healthy controls.

This observation is consistent with previous research indicating a potential role for vitamin D in autoimmune diseases. Vitamin D is known to modulate immune responses, and its deficiency has been implicated in various autoimmune conditions, including AA.

The pathophysiology of AA may entail dysregulated immunological responses, which could explain the decreased serum vitamin D levels observed in these patients.

Our investigation did not uncover a significant correlation between serum calcium levels and AA, which was unexpected. Although calcium is necessary to preserve the structure and function of hair follicles, its lack of correlation with AA raises the possibility that calcium levels, in contrast to vitamin D, may not be as important to the pathophysiology of AA.

Sensitivity analysis demonstrated the durability of our results by producing consistently identical results even after methodically eliminating individual research. This indicates the reliability and stability of our results.

Furthermore, the absence of publication bias in our meta-analysis enhances the credibility of our findings. The lack of skewed outcomes due to selective reporting or publication bias reinforces the validity of the observed associations between AA and serum vitamin D levels.

Overall, our meta-analysis underscores the importance of considering vitamin D status in the management of AA.For AA patients, vitamin D deficiency screening and therapy may have therapeutic benefits.To clarify the underlying mechanisms that connect vitamin D insufficiency to AA and investigate the possible therapeutic consequences of vitamin D supplementation in AA therapy, more research is necessary.

Conclusion

As a result, our meta-analysis sheds important light on the relationship between vitamin D insufficiency and AA, emphasizing the possible involvement of vitamin D in the pathophysiology and treatment of AA. Subsequent investigations ought to concentrate on verifying these results and investigating the medicinal possibilities of vitamin D administration in AA therapy approaches.

Funds

No funding

Conflict of interest

Nill

Permission

Taken from ethical committee

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