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Original Article

Serum Vitamin D levels in males with premature androgenetic alopecia: a prospective case-control study

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Abstract

Introduction: Androgenetic alopecia (AGA), the predominant form of hair loss, affects a significant global population. While emerging research suggests a potential correlation between serum vitamin D levels and AGA severity, the current body of evidence remains inconclusive, necessitating further investigation to elucidate this relationship and its clinical implications.

Objective: To evaluate serum vitamin D levels in AGA patients and explore their relationship with the condition's severity.

Materials and methods: A seven-month prospective case-control study was carried out in Pakistan. Male participants aged 18-30 yeas were divided into AGA patients and matched controls. AGA severity was assessed using the Norwood-Hamilton classification, and serum vitamin D levels were measured via radioimmunoassay. Statistical analysis included chi-squared, Fisher's exact, and unpaired t tests.

Results: Patients with AGA had significantly lower sun exposure and higher rates of vitamin D deficiency (84% vs. 22%, p<0.0001) compared to controls. These patients had a higher BMI (24.68±3.18 vs. 22.89±2.80, p=0.0035). Their serum vitamin D levels were significantly lower in patients (45.64±29.99 nmol/L) than controls (91.93±30.55 nmol/L, p<0.0001). A strong association was found between vitamin D deficiency and AGA (p<0.001). Vitamin D levels correlated with the severity of AGA, and ROC analysis showed high diagnostic accuracy (AUC=0.89, p<0.0001).

Conclusion: Serum vitamin D levels show a significant inverse association with AGA, with substantially lower concentrations and higher deficiency rates in patients compared to controls. The observed correlation between vitamin D levels and AGA severity suggests potential therapeutic implications for vitamin D supplementation in the management of AGA.

Keywords

androgenetic alopecia, case-control study, hair loss, male pattern baldness, vitamin D deficiency

Introduction

Alopecia is characterized by hair loss on different parts of the body and can be divided into two main types: scarring and non-scarring alopecia.[1] Androgenetic alopecia (AGA), the most common form of hair loss in both sexes, is a non-scarring pattern alopecia that affects millions of people worldwide. It manifests as a progressive reduction in hair diameter and follicular density, primarily affecting the vertex and bitemporal regions of the scalp. The phenotypic expression of AGA is sex-specific, with different patterns observed in males (MAGA) and females (FAGA).[2] The term premature or early-onset AGA is generally applied to cases manifesting before the third or fourth decade of life, typically before the age of 30 years.[3] Conversely, AGA presenting after the fifth decade is conventionally categorized as later-onset disease.[2] This variability in age criteria highlights the need for a standardized definition to facilitate consistent research and clinical approaches to the management of early-onset AGA.[4] The prevalence of AGA shows significant demographic variability and age-dependent progression. While the incidence of AGA generally correlates with age, early-onset cases represent a substantial proportion, with reported prevalence ranging from 19.2% to 57.6% across diverse populations.[3,5] In Caucasian cohorts, AGA manifestation reaches significant levels by the seventh decade, affecting approximately 80% of males and 50% of females.[6] Interestingly, while Asian populations have historically had a lower prevalence of AGA, recent epidemiological data suggest an upward trend in incidence.[7]

The impact of AGA extends beyond its physical manifestations, significantly affecting patients' psychosocial well-being and quality of life.[3] The condition's visibility and cultural associations with youth and vitality often lead to profound psychological sequelae. Affected individuals frequently report experiencing physical dissatisfaction, emotional distress, and perceived social rejection.[8] Moreover, studies have documented a higher prevalence of low self-esteem, anxiety, and depression among AGA subjects.[9] Early-onset AGA is associated with significant systemic health implications. Studies have linked AGA to metabolic syndrome and its components.[10] Moreover, premature AGA correlates with increased cardiovascular risk, as evidenced by associations with insulin resistance markers[11], carotid atherosclerosis[12], and ischemic heart disease[13]. The literature has also reported an association with benign prostatic hyperplasia.[14]

The etiology of AGA is multifactorial, involving genetic predisposition, hormonal influences, and environmental factors. While androgens, particularly dihydrotestosterone (DHT), play a crucial role in AGA pathogenesis by affecting dermal papilla cells and causing hair follicle miniaturization, other factors such as chronic micro-inflammation and oxidative stress contribute to its development.[15,16] Recent research has highlighted the potential role of vitamin D in AGA. Vitamin D, synthesized in the skin and obtained through diet, exerts immunomodulatory effects via vitamin D receptors (VDRs) in immune cells and hair follicle keratinocytes.[17] Studies have reported associations between vitamin D deficiency and various hair disorders, including AGA.[18] Its influence on adipocytokine secretion, metabolism regulation, inflammation, and oxidative stress balance suggests its potential involvement in AGA onset and progression.[19] However, the relationship between vitamin D and AGA, particularly in men, remains controversial. While some studies have found correlations between serum vitamin D levels and AGA severity, others suggest limited evidence for this association.[20] The discrepancy in findings indicates that additional factors may modulate this relationship. Given the irreversible nature of hair follicle miniaturization in AGA, early prevention and treatment are crucial.[7] Although the evidence for vitamin D's role in AGA is inconclusive, its importance in maintaining skin homeostasis and potential anti-inflammatory effects warrant consideration.[21,22] Studies have reported lower vitamin D levels in patients with hair loss compared with healthy controls, suggesting a potential benefit of vitamin D supplementation in AGA management.[7]

Emerging research suggests a link between serum vitamin D levels and AGA, though evidence remains limited, particularly in regions with prevalent vitamin D deficiency. This study evaluates serum vitamin D in young male AGA patients and explores its relationship with disease severity in Pakistan, where data is scarce. Additionally, the role of androgen levels and micronutrient status in AGA remains unclear, underscoring a knowledge gap. By examining vitamin D's role in AGA progression, this study may provide insights that in-form diagnostic and therapeutic approaches, advancing the understanding and management of AGA.

Materials and methods

Study design, site, and population

This was a hospital-based prospective case-control study conducted at the Department of Dermatology, Pakistan Navy Ship Shifa Hospital, Karachi, Pakistan, for over seven months, from March to August 2023. The sample size was determined using OpenEpi based on relevant research literature.[4] The study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Participants grouping and study criteria

Samples were selected using a random sampling technique. Subjects were categorized into two groups: the control group and the patient group, as illustrated in **Fig. 1**.

Participants in the patient group were males aged 18 to 30 years with a clinical diagnosis of androgenetic alopecia. An equal number of healthy male controls, matched for age, socioeconomic status, and outdoor exposure, were

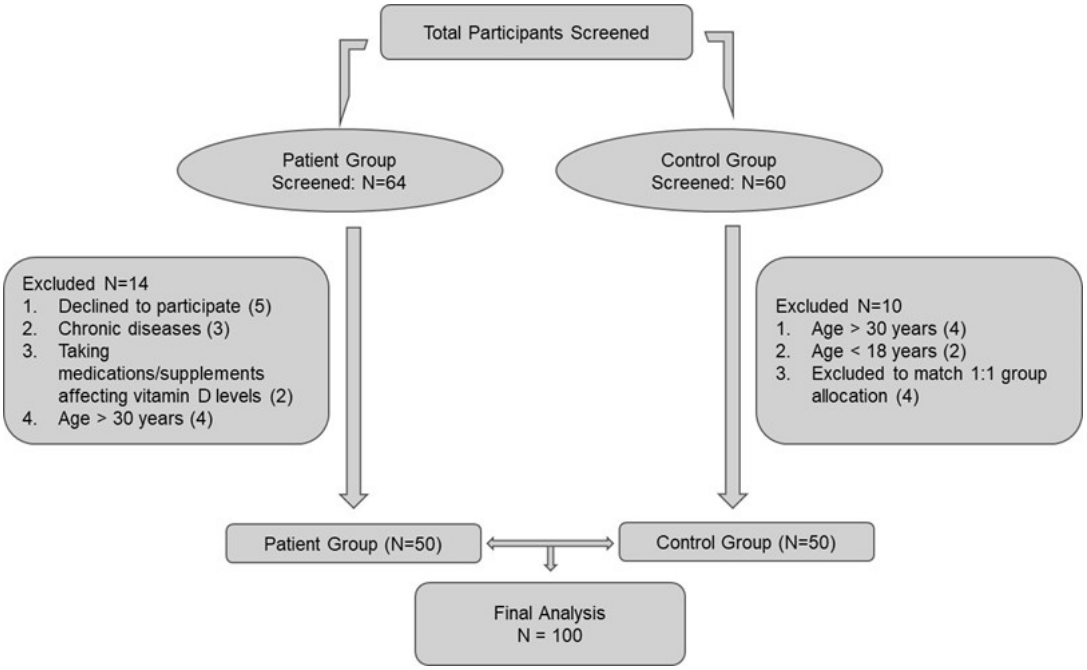

Figure 1. Patient flow chart.

recruited from volunteers attending the Dermatology Outpatient Department during the study period. Exclusion criteria included patients who refused to participate, those with a history of drug abuse, or those diagnosed with chronic illnesses, psychiatric disorders, or other scalp hair disorders such as alopecia areata, trichotillomania, tinea capitis, and traction alopecia. Individuals with clinical or biochemical evidence of hyperandrogenemia, those taking medications or supplements that could alter serum vitamin D levels (e.g., systemic corticosteroids, antiepileptic drugs, cholesterol-lowering drugs), and those with malabsorption disorders, nutritional deficiencies, or kidney, liver, or bone diseases were also excluded from the study.

Data collection tool and instruments

Data were collected using a detailed questionnaire that included demographic information such as age, sex, socioeconomic status, and measurements like height, weight, and body mass index (BMI). Participants provided information about their occupation, mainly focusing on factors that might affect sun exposure, such as working or engaging in outdoor activities. The questionnaire also asked about sun exposure habits, estimating the time spent outdoors during daylight hours based on participants' self-reports. The questionnaire covered a comprehensive medical history, including past or current health conditions, medications, and family history of androgenetic alopecia or related conditions. A thorough record of medication use was taken to identify any drugs that might influence hair growth or vitamin D levels. Participants also underwent a general physical examination to assess their overall health. To assess the type and severity of androgenetic alopecia, the Norwood-Hamilton classification system instrument was used to categorize patients.[8]

Laboratory parameters

Blood samples were collected from each patient using standard venipuncture techniques. Following collection, the blood samples were immediately placed into serum separator tubes and allowed to clot at room temperature for 30 minutes. The samples were then centrifuged at 1500×g for 10 minutes to separate the serum. The serum was carefully aliquoted into sterile, labelled cryovials and stored at -80°C until further analysis. Serum vitamin D levels were measured using a highly sensitive and specific radioimmunoassay, following the standard protocols. The assay's precision and accuracy were verified by including quality control samples with known vitamin D concentrations in each assay run. Vitamin D levels were categorized based on established clinical guidelines into three groups: deficiency (<25 nmol/L), insufficiency (25–75 nmol/L), and sufficiency (75–250 nmol/L).

Statistical analysis

Data were stored and analyzed using IBM SPSS version 25.0 and GraphPad Prism version 8.1. The normality of the data was assessed with the Shapiro-Wilk test. Categorical variables were presented as frequencies and percentages, while continuous variables were expressed as means and standard deviations. Categorical variables were analyzed using chi-squared or Fisher's exact tests, including alopecia severity, hair loss site, AGA, and vitamin D level reference ranges. Unpaired t-tests were conducted to compare the means of continuous variables, such as age, BMI, and serum vitamin D levels (nmol/L),

between the patient and control groups. Spearman's rho test was used to assess correlations, and a heat map was generated to visualize the strength of these relationships. The ROC curve was employed to visualize the area under the curve. Data was visually presented using bar charts or box plots with whiskers. Statistical significance was set at $p<0.05$, with a 95% confidence interval.

Ethical approval and consent to participate

The study followed the ethical guidelines set by institutional and national research committees and the principles of the Helsinki Declaration. Ethical approval was granted by the Pakistan Navy Ship Shifa Hospital's Ethical Review Committee (reference No ERC/2023/Derm/02). Written, informed, and voluntary consent was obtained from all participants. Data was coded to ensure confidentiality and was accessible only to the principal investigator.

Results

Out of a total of 100 participants in the study, there were equal numbers of patients (50%) and healthy controls (50%). The mean age of controls and patients were 23.28±4.10 and 24.42±3.87 years, respectively. Significant differences were observed between the patient and control groups across several variables.

The patient group had a higher percentage of married individuals (62% vs. 40%, p=0.04) and more people earning over 50,000 PKR (64% vs. 36%, p=0.02). While occupation and residential status were similar, patients had higher levels of graduation education (44% vs. 24%, p=0.06). Daily sun exposure was significantly lower in patients, with only 4% having more than 6 hours compared to 34% in controls (p=0.00). Vitamin D deficiency was notably higher in the patient group (84% vs. 22%, p<0.0001). These differences underscore the socioeconomic and clinical disparities between the groups **(Table 1)**.

Vitamin D status differed by group (p<0.001): 36% of patients were deficient, 48% insufficient, and 16% were sufficient, while controls had no deficiencies, 22% insufficiency, and 78% sufficient. All deficient and most insufficient participants were in the patient group, while 83% of those with sufficient levels were in the control group **(Fig. 2)**.

The distribution of vitamin D levels among patients with different initial hair loss sites and family history did not show statistically significant differences. Vitamin D insufficiency was common across all hair loss sites, with the temporal region showing 52.9% insufficiency (p=0.175). Similarly, patients without a family history had slightly higher vitamin D sufficiency (23.1% vs. 8.3% with a family history, p=0.352) **(Table 2)**.

Vitamin D levels varied significantly across AGA grades (p=0.002). Most patients with stage II alopecia had suffi-

Table 1. Comparison of demographic and clinical characteristics between patient and control groups, chi-square test.

Variables		Patients (50)	Control (50)	*p*-value
		Frequency (%)		
Marital status	Married	31 (62%)	20 (40%)	0.04
	Unmarried	19 (38%)	30 (60%)	
Monthly income (PKR)	Less than 20,000	1 (2%)	3 (6%)	0.02
	Between 20,000 and 50,000	17 (34%)	29 (58%)	
	More than 50,000	32 (64%)	18 (36%)	
Occupation type	Indoor	30 (60%)	36 (72%)	0.29
	Outdoor	20 (40%)	14 (28%)	
Residential status	Rural	6 (12%)	13 (26%)	0.12
	Urban	44 (88%)	37 (74%)	
Education	Illiterate	1 (2%)	0 (0%)	0.06
	Primary	4 (8%)	3 (6%)	
	Secondary	2 (4%)	9 (18%)	
	Higher Secondary	21 (42%)	26 (52%)	
	Graduation	22 (44%)	12 (24%)	
Average sun exposure (hrs)	Less than 1 hour	15 (30%)	12 (24%)	0.00
	Between 1 to 6 hours	33 (66%)	21 (42%)	
	More than 6 hours	2 (4%)	17 (34%)	
Vitamin D levels (nmol/L)	Low	42 (84%)	11 (22%)	<0.0001
	Normal	8 (16%)	39 (78%)	

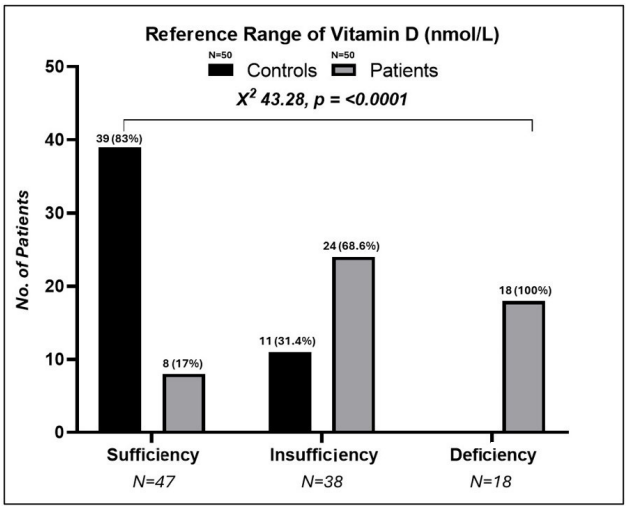

Figure 2. Distribution of vitamin D status among cases and controls.

cient vitamin D (100%), while those with stages IV and V had higher rates of deficiency (50% and 81.8%, respectively). Stages II (A) and III (A) showed a mix of insufficiency and sufficiency, with no deficiency reported. These results indicate a clear association between alopecia stage and vitamin D levels **(Fig. 3)**.

The comparison between control and patient groups revealed significant differences in BMI and serum vitamin D levels but not in age. The patient group had a higher mean BMI (24.68±3.18) than controls (22.89±2.80), with a statistically significant p-value of 0.0035. Serum vitamin D levels were significantly lower in patients (45.64±29.99 nmol/L) than in controls (91.93±30.55 nmol/L), with a p-value of <0.0001, as shown in **Table 3** and **Fig. 4.** These findings indicate that patients had higher BMI and lower vitamin D levels than controls.

Table 4 shows a strong positive correlation between the age of disease onset and age (r=0.86, p<0.001). There was also a moderate positive correlation between age of onset and vitamin D levels (r=0.35, p=0.012), suggesting higher vitamin D is associated with later-onset disease. For disease duration, there was a moderate positive correlation with age (r=0.32, p=0.022) and a moderate negative correlation with vitamin D levels (r=−0.55, p<0.001). The receiver

Table 2. Association of vitamin D levels with initial site of hair loss and family history, chi-square test, 95% confidence interval, androgenetic alopecia (AGA)

Variables		Vitamin D levels (nmol/L) Reference range			*p*-value
		Deficiency	Insufficiency	Sufficiency	
Initial site of hair loss	Frontal	6 (37.5%)	8 (50%)	2 (12.5%)	0.175
	Temporal	3 (17.6%)	9 (52.9%)	5 (29.4%)	
	Vertex	9 (52.9%)	7 (41.2%)	1 (5.9%)	
Family history of AGA	No	9 (34.6%)	11 (42.3%)	6 (23.1%)	0.352
	Yes	9 (37.5%)	13 (54.2%)	2 (8.3%)	

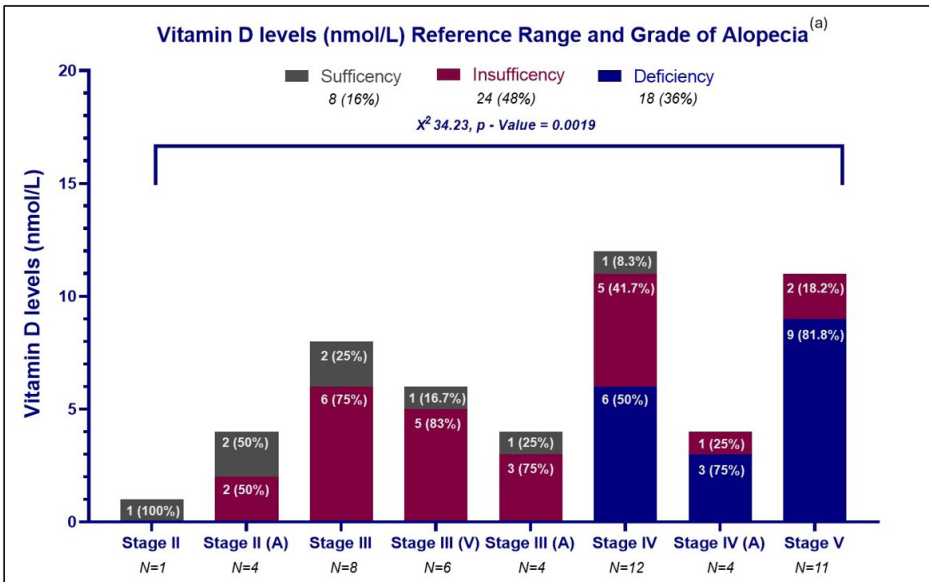

Figure 3. Distribution of vitamin D levels across different grades of alopecia. (a) Androgenetic alopecia classification according to Hamilton-Norwood scale.

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Table 3. Comparison of age, BMI, and serum vitamin D levels between control and patient groups, unpaired t-test, 95% confidence interval

Variables	Controls		Patients		95% CI	p-value
	Mean±SD	Minimum - Maximum	Mean±SD	Minimum - Maximum		
Age	23.28±4.10	18–30	24.42±3.87	18–30	−0.4437 to 2.724	0.1563
BMI	22.89±2.80	18.3–30	24.68±3.18	17.8–35.4	0.6030 to 2.985	0.0035
Serum vitamin D levels (nmol/L)	91.93±30.55	42.3–163.5	45.64±29.99	18–186	−58.31 to −34.28	<0.0001

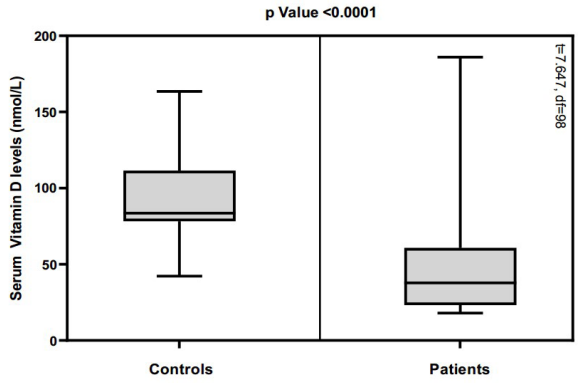

Figure 4. Serum vitamin D levels (nmol/L) in patients and controls.

operating characteristic curve analysis for serum vitamin D levels yielded an area under the curve of 0.89 (95% CI: 0.8286–0.9574), with a p-value <0.0001 **(Fig. 5)**.

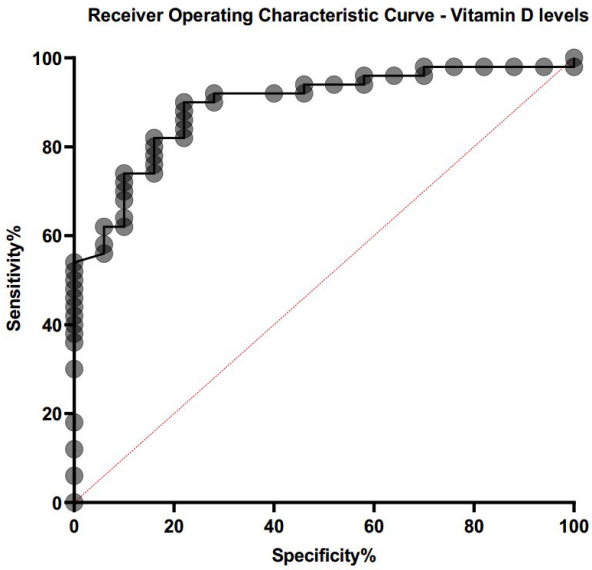

Figure 5. ROC curve for serum vitamin D levels (nmol/L).

Table 4. Correlation matrix of disease onset, duration, age, and vitamin D levels, Spearman's rho test

Variables	Age at onset of disease	Duration of disease	Age
Duration of disease	p=0.401, r=−0.12 95% CI: [−0.3937–0.1709]		
Age	p<0.001, r=0.96 95% CI: [0.7541–0.9172]	p=0.022, r=0.32 95% CI: [0.03863–0.5562]	
Vitamin D levels (nmol/L)	p=0.012, r=0.35 95% CI: [0.07113–0.5783]	p<0.001, r=−0.55 95% CI: [−0.7254 - −0.3188]	p=0.887, r=0.02 95% CI: [−0.2672–0.3048]

Discussion

Over a billion children and adults worldwide suffer from vitamin D insufficiency and inadequacy, making it a global health concern.[23] Vitamin D deficiency negatively impacts skeletal health and calcium regulation, reducing bone mineralization and heightening fracture risk. Additionally, it is associated with various non-skeletal conditions, including neoplasms, autoimmune disorders, cardiac diseases, and muscular atrophy.[24] The increased prevalence of this vitamin D deficiency stems from multiple factors: more significant use of photoprotective agents, extended indoor time, age-related epidermal changes, reduced dairy intake, rising obesity rates, and specific medication use.[25]

Our study included 50 male patients with androgenetic alopecia (AGA), with a mean disease duration of 27.64±17.836 months and an average age of onset at 22.02±3.645 years. Vitamin D deficiency was much more common in patients compared to the control group. Patients had significantly lower serum vitamin D levels (45.64±29.99 nmol/L) than controls (91.93±30.55 nmol/L),

with p<0.0001. Among the patients, 36% were vitamin D deficient, 48% were insufficient, and 16% had sufficient levels. Notably, all participants with vitamin D deficiency were in the patient group. Across various case-control studies, including ours, a consistent trend of lower vitamin D levels in patients with AGA compared to controls is observed. Our study, involving 50 male patients, found significantly lower serum vitamin D levels in patients compared with the controls. Similarly, Sanke et al. reported lower levels in AGA patients (20.10±4.8 ng/mL) than in controls (29.34±5.6 ng/mL).[4] Tahlawy et al. found a difference in vitamin D levels between patients (37.1±11.9 ng/mL) and controls (44.2±9.6 ng/mL).[26] Saraç et al. also reported lower levels in patients (12.2±8.3 ng/dL) compared to controls (16.02±8.3 ng/dL).[27] Zhao et al. observed a more negligible difference in a large cohort, with patients having 50.00 nmol/L and controls 53.05 nmol/L.[17] These findings collectively indicate that AGA patients generally have lower vitamin D levels than controls, as shown in **Table 5**.

Hair follicles are sensitive to hormones, including vitamin D, which is important for calcium metabolism, immune system regulation, and cell growth and differentiation.[31] The active form of vitamin D binds to vitamin D receptors (VDRs) in target cell nuclei, regulating vitamin D-responsive genes.[32] VDRs are present in the outer root sheath (ORS), hair follicle bulb, and sebaceous glands, where they regulate skin biology, including epidermal proliferation and differentiation. Studies also show VDRs are crucial for normal hair cycling, especially initiating the anagen phase.[32,33] Fawzi MM and colleagues studied 20 androgenetic alopecia patients to evaluate the role of vitamin VDRs in skin and blood. They found that serum and tissue VDR levels were significantly lower in AGA patients than in controls (p=0.000).[34] Animal studies consistently reveal that activating the VDRs is critical for managing the hair follicle cycle, particularly during the growth phase (anagen), as well as regulating the synthesis of

Table 5. Comparison of vitamin D levels in androgenetic alopecia (AGA): a review of case-control studies

Author	Study design	Sample size Number of Patients	Population	Vitamin D levels in cases	Vitamin D levels in controls	p-value
(a) Our study	**CCS**	**50**	**Male**	**45.64±29.99 nmol/L**	**91.93±30.55 nmol/L**	**<0.0001**
(b) Sanke S, et al.[4]	CCS	50	Male	20.10±4.8 ng/mL	29.34±5.6 ng/mL	<0.001
(c) Tahlawy SM, et al.[26]	CCS	30	Male	37.1±11.9 ng/mL	44.2±9.6 ng/mL	0.01
(d) Saraç G, et al.[27]	CCS	58	Male and female	12.2±8.3 ng/dL	16.02±8.3 ng/dL	0.01
(e) Zhao J, et al.[17]	CCS	777	Male	50.00 nmol/L [48.90, 51.40]	53.05 nmol/L [51.55, 54.60]	0.0005

[a-e] All studies consistently demonstrated significantly lower vitamin D levels in AGA patients compared to controls (p<0.05); (a) Showed the largest difference in vitamin D levels between cases and controls, with AGA patients having approximately 50% lower levels than controls; (a-c, e) Four out of five studies focused exclusively on male subjects, (e) with only one study including both genders. Study populations ranged from 30 to 777 subjects,(e) with conducting the largest investigation in a Chinese Han population. Values are presented as mean±SD or median (quartiles). CCS: case-control study

Moreover, a significant negative correlation between vitamin D levels and BMI was observed, suggestin that obesity may influence vitamin D status. Since vitamin D is lipid-soluble, adipose tissue is believed to sequester it, reducing the amount available for physiological and metabolic processes. Wortsman et al. suggest that while obesity does not affect the skin's ability to produce vitamin D3, it may hinder its release into circulation due to increased sequestration by subcutaneous fat.[28] This indicates that obese individuals may need higher doses of vitamin D to compensate for lower levels.

The severity of AGA is commonly assessed using the Hamilton-Norwood scale (HNS) in men[29] and the Ludwig classification in women[30]. Using the HNS, we found significant variation in vitamin D levels across AGA stages. All stage II patients had sufficient levels, while stages IV and V showed higher deficiency rates (50% and 81.8%, respectively). Stages II (A) and III (A) had a mix of insufficiency and sufficiency, with no deficiencies.

follicle-specific genes.[35] Furthermore, vitamin D3 has been shown to stimulate the ultimate differentiation of human hair follicles.[36] Nichols et al. studied patients with AGA who were given a cholecalciferol supplement. They found a positive correlation between the improvement in terminal hair count and the hair mass index.[37] Similarly, an animal study on nude mice found through histological examination that supplementation with vitamin D3 analogues stimulated the development of hair follicles.[38] In a 2015 study, 48 patients were treated with topical calcipotriol for 12 weeks, resulting in a positive response in 69.2% of patients (p=0.001).[39] These findings provide significant knowledge of the possible involvement of vitamin D in the pathogenesis of AGA. The efficacy and safety of vitamin D and its analogues as treatments for AGA remain to be entirely determined. However, most studies agree that topical and oral vitamin D supplements can significantly improve AGA.[40] Further research is needed, especially clinical tri-

als, to understand better the complex relationship between vitamin D status and body composition.

Our study provides novel insights into the relationship between vitamin D deficiency and premature AGA in young males, an underexplored demographic in this geographical region. The significantly higher rates of vitamin D deficiency in AGA patients, correlated with disease severity, suggest potential therapeutic implications. These findings underscore the need for increased vitamin D screening and supplementation as adjunct interventions to manage this condition.

Conclusion

Our study reveals a significant relationship between vitamin D insufficiency and early-onset AGA in young males. Patients exhibited lower serum vitamin D levels than healthy controls, with a high prevalence of vitamin D deficiency and insufficiency. We identified reduced sun exposure and higher BMI as potential risk factors. Future research directions include randomized controlled trials exploring vitamin D supplementation as a potential therapy and investigating genetic factors affecting vitamin D metabolism. These findings provide a foundation for understanding the pathophysiology of premature AGA in men and may lead to new treatment strategies.

Strengths and limitations

This study presents several methodological strengths alongside notable limitations. The case-control design facilitated a detailed comparison of vitamin D levels between cases and controls, with the sample size providing adequate statistical power to detect significant differences. However, certain limitations warrant consideration. Firstly, the sample, while sufficient for our primary analyses, was relatively modest in size and sourced from a single center, potentially limiting the generalizability of our findings. Secondly, our analytical approach did not account for potential seasonal variations in vitamin D levels, which may have influenced inter-group comparisons. Lastly, the study's scope did not extend to examining VDR expression or polymorphisms. These limitations underscore the need for more extensive, multi-center studies incorporating seasonal adjustments and molecular analyses.

Author contributions

Conceptualization: R.B. and S.K.; writing of initial drafts: R.B., H.A., S.M.A., M.S.H., and H.A.; review and editing: R.B., S.K., H.A., M.R.S., and H.F.; project supervision: R.B., S.K., and H.A.; data curation: R.B., H.A., and M.S.H.; software: M.R.S.; data analysis: R.B. and M.R.S.; resources: M.R.S., S.A.S., and H.F.; All authors approved the final manuscript before submission to the journal. All authors have contributed signifi cantly to this publication.

Competing Interests

The authors have declared that no competing interests exist.

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