International Journal of Dermatology, Venereology and Leprosy Sciences

E-ISSN: 2664-942X
P-ISSN: 2664-9411
Impact Factor (RJIF): 5.67
www.dermatologypaper.com
Derma 2025; 8(2): 105-113
Received: 20-06-2025
Accepted: 23-07-2025

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Scalp hair cortisol concentration in patients with alopecia areata and correlate its level with the disease variables

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DOI: https://www.doi.org/10.33545/26649411.2025.v8.i2b.249

Abstract
Alopecia areata (AA) is a chronic, immune-mediated condition characterized by nonscarring hair loss (HL) due to targeting of anagen hair follicles. It typically manifests as smooth, well-defined bald patches on scalp but can also affect other hair-bearing regions, including eyelashes, extremities, eyebrows, and beard. Severe cases may result in complete loss of all body hair (alopecia universalis) or scalp hair (alopecia totalis). Relationship between psychosocial stress and AA remains debated. Some studies suggest a higher prevalence of psychiatric comorbidities, like depression and, anxiety among individuals with AA. Research indicates that substance P and nerve growth factor play an essential role in stress-related hair growth inhibition in mice and may contribute to AA pathogenesis. Furthermore, AA patients may demonstrate increased hypothalamic-pituitary-adrenal axis activity, which controls stress response, potentially affecting their capacity to manage stressors. Cortisol, a glucocorticoid hormone secreted by adrenal glands, rises in response to stress. Studies commonly assess stress using cortisol levels and Perceived Stress Scale, However, cortisol measurements from blood, saliva, or urine reflect acute stress responses and may not accurately indicate chronic stress. Cortisol in the hair can be utilized as a valid biomarker for chronic stress, as human hair grows at an average about rate 1 centimeter every month.
This review article aimed to examine scalp hair cortisol concentration in cases had AA and correlate its level with the disease variables.

Keywords: Scalp hair, cortisol, alopecia areata

Introduction
Alopecia areata (AA) is an autoimmune disease which is relapsing and remitting and is mediated by T cells. It is indicated by circular, non-scarring hair loss (HL) areas that exhibit varying degrees of severity. According to estimates, AA has a lifetime prevalence of 2.1% and can appear at any age in genetically predisposed people in reaction to unidentified environmental stimuli. Any place that bears hair may be impacted, however the scalp is the most affected. Patients are at an elevated developing psychiatric comorbidities risk, such as depression, social phobia, anxiety, and suicidal ideation, which may significantly compromise their health-related life quality. The clinical trajectory of AA is unpredictable and clinically heterogeneous. Alopecia universalis (AU) or alopecia totalis (AT) may be experienced by patients in severe cases, which can lead to complete HL on cranium or torso. HL that spontaneously returns within a year is considered acute AA, whereas HL that lasts longer than a year is considered chronic AA. Chronic AA is present in one-third of patients, and 45% of them will progress to AT or AU. Refractory disease is more likely to occur in individuals with comorbid atopic disease, an ophiasis distribution, extensive HL (>50% of the scalp), nail involvement, earlier onset age, and a poor prognosis. Additionally, atopic disorders and other autoimmune diseases are more likely to occur in AA patients. In addition, the pathogenesis of AA has been linked to hair follicle immune privilege collapse. Treatment of AA is the primary objective to halt progression of disease and reverse hair loss. This article reviews, we offer a concise summary of clinical characteristics of AA, investigate the pathogenesis of the disease, and examine both established and emerging therapeutic strategies [1, 2].

Epidemiology

The incidence of AA over the course of one's lifespan is between 0.7% and 4.0%. Even though individuals of all ages may be affected, the majority of sufferers (82.6%-88%) experience their first episode at 40 years old. The average age at which pediatric patients beneath the age of 16 are diagnosed is 11.2 years. In spite of the absence of gender predilection, a cross-sectional study conducted by Lee *et al*. on a US population revealed that African Americans had a higher likelihood of AA, while Asians had a lower likelihood as compared to whites. Moreover, a family history of AA is reported in 10-51.6% of pediatric patients and up to 8.6% of adult patients. Autoimmune thyroid disease, systemic lupus erythematosus (SLE) risk after a diagnosis of AA. In 39% of cases, AA patients are diagnosed with co-morbid atopic disease [3].

Clinical features

There are numerous patterns in which AA may manifest, as it is a clinically heterogeneous condition. The typical presentation is a non-scarring, discrete, well-defined region of HL (Figure 1). Occasionally, skin may be slightly erythematous, but there is no epidermal change. It is smooth, resembling the bottom of an infant. Draw tests at an AA lesion margin are positive in the presence of active disease, which leads to the development of telogen or dystrophic anagen hairs. Following this, the clinical trajectory is unpredictable. Additional patches may develop at variable intervals, or An initial patch may be extended over a duration from weeks to months. Indeed, developing risk additional patches may be elevated by solitary patch presence, which is most prevalent initial presentation. It is possible for new patches to coalesce in the future to create larger patches. Prodromal localized dysesthesia is a symptom that some patients experience anterior to the development of an AA lesion; HL is generally asymptomatic [4].

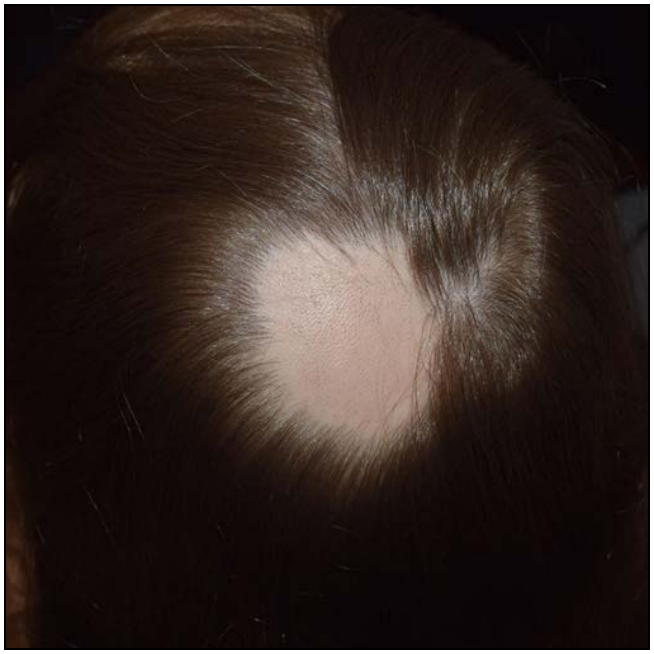

Fig 1: Example of acute patch of AA affecting the occiput [5]

Hair and scalp dermatoscopy, also referred to as trichoscopy, may be employed to facilitate the diagnosis of AA and to monitor disease activity (Table 1). Tapered hairs, broken hairs, exclamation point hairs, and black spots are among trichoscopic characteristics of active AA. Characteristics of long-standing AA include short vellus hairs and yellow spots [6, 7].

Table 1: Trichoscopic findings in AA and their significance [8]

Sign	Description/Etiology	Significance
Yellow Dots	Distention of the affected follicular infundibulum with keratinous material and sebum	Sensitive sign of AA. Supports presence of non-scarring alopecia
Short Vellus Hairs	Thin and nonpigmented hairs	Sensitive sign of AA. Supports regrowth when seen in AA
Black Dots	Broken pigmented hair at the level of the scalp	Specific for AA. Supports presence of active disease. Negative predictive marker for regrowth
Exclamation Mark Hairs	Pigmented short (≤1.2mm) hairs with wide distal shaft diameter that thins proximally	Associated with active disease. Lymphocytic inflammatory activity affecting the hair bulb. Negative predictive marker for regrowth
Tapered Hairs	Longer exclamation mark hairs	Negative predictive marker for regrowth
Upright Regrowing Hairs	Tapered end that thickens proximally, thicker than vellus hairs	Can be seen in many conditions. Positive predictive marker for regrowth
Pigtail Hair	Short, regularly twisted hairs with short tapered end	Positive predictive marker for regrowth
Pohl-Pinkus Constrictions	Hairs with segmental thinning (constriction) or narrowing	Not specific for AA. Presence of multiple segments supports cyclical disease activity

It is anticipated that 40% of cases had AA will only ever grow a single patch, spontaneously regenerate through six months if left untreated. Additional areas will develop in 27% of patients. (Figure 2-Figure 3) even though they still attain complete remission after one year. On the other hand, a lot of cases will experience a relapse through months or years following remission. The total HL risk on scalp (AT) is 30% for patients with chronic AA, and of losing all hair on body risk (AU) is 15%. This is the case when patches persist for more than one year (Figure 4). An ophiasis distribution, which is distinguished by a band-like HL that extends across occipital cranium, may also be a manifestation of HL in AA. (Figure 5). A sisaipho, or inverse ophiasis pattern, has also been identified. HL in temporal,frontal, and parietal scalp is a feature of this AA pattern, which is comparable to male androgenetic alopecia. The scalp periphery is unaffected. Diffuse AA, which is frequently referred to as AA incognita, may occasionally be observed in patients hadn't any discrete regions (Figure 6) [1].

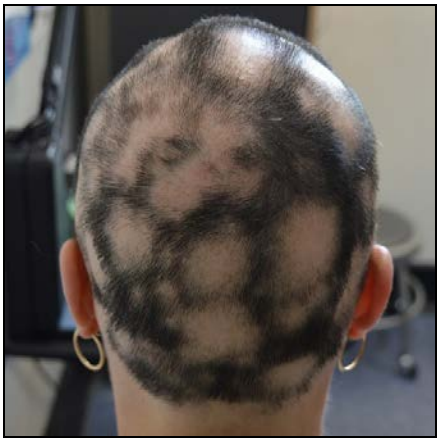

Fig 2: Example of patchy AA [8]

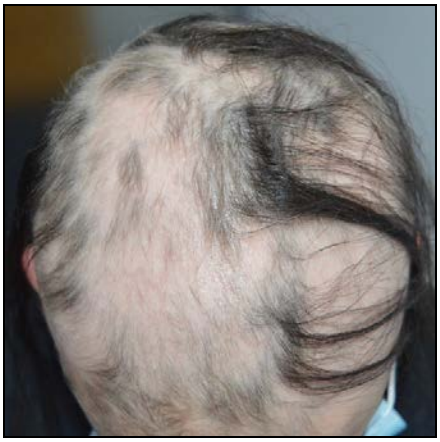

Fig 3: Example of patchy AA with mixed areas of regrowth and coalescing patches [8]

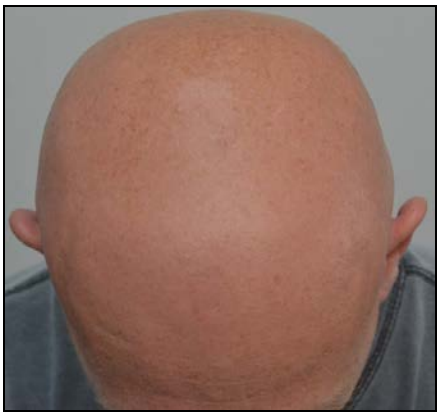

Fig 4: Example of AT [8]

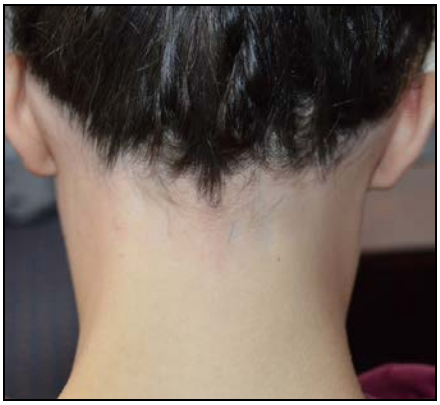

Fig 5: Example of ophiasis type AA [8]

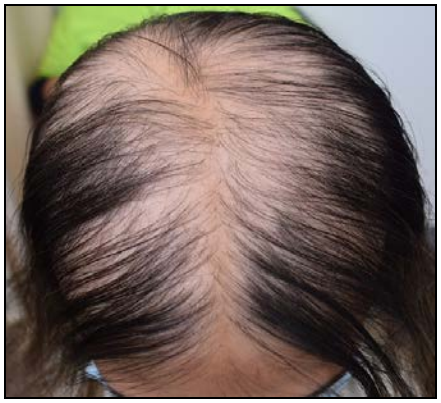

Fig 6: Example of acute diffuse AA [8]

Even though AA can affect any hair-bearing site cranium is most susceptible to AA and is often first site to develop a lesion. eyelash and Eyebrow loss are prevalent, and 28% of males experience beard loss. In contrast to pigmented hairs, white hairs seem to be relatively safe in AA for reasons that are not completely understood. hair reports "turning white overnight" (canities subita) in patients with accelerated disease progression may be attributable to this phenomenon. Furthermore, we have observed that AA is unusual in redheads; in fact, red hair may operate as a protective factor anti AA. AA is a non-scarring alopecia, meaning that it does not obliterate hair follicles (HFs). Consequently, hair regrowth may occur for an extended period, potentially for the rest of one's life. Regrowth occurs within patches with hairs that are usually white and fine but gradually become thicker and re-pigmented (Figure 7). AA progression and regrowth can occur in distinct regions of the cranium at the same time, which is important [4].

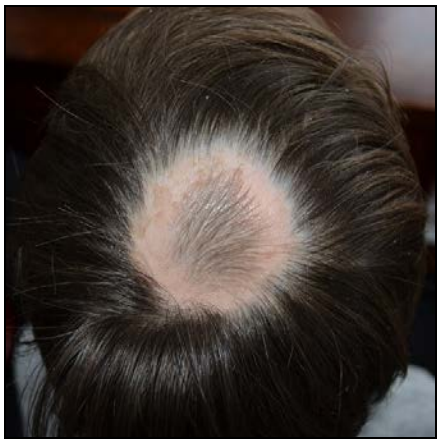

Fig 7: Example of regrowth of hair within an AA patch [8]

Active HL may precede, succeed, or coincide with nail disease, which constitutes 10-15% of cases of AA. Nail involvement may encompass red patches on the lunulae, onychorrhexis, trachyonychia, punctuate leukonychia, onycholysis, and onychomadesisDue to its correlation with AT and, AU nail involvement may be measured a reduced prognostic factor [9].

Histopathology

Depending on stage of disease, histopathology will vary. A peribulbar lymphocytic infiltrate, consisting of CD8+ T-cells and CD4+, is observed around anagen follicles in the

acute and subacute stages, approximating a "swarm of bees" pattern (Figure 8). Furthermore, the follicle endures miniaturization, which leads to a transition from catagen hair growth stage to telogen phase (resting phase). macrophages, apoptosis, foreign body giant cells, and microvesiculation may be observed in of HFs vicinity. Telogen or catagen number hairs rises, and pigmentary incontinence is observed. The inflammation may or may not resolve during the chronic stage. The anagen hair count (actively growing hair) rises, and inflammation is minimal during the recovery stage [10].

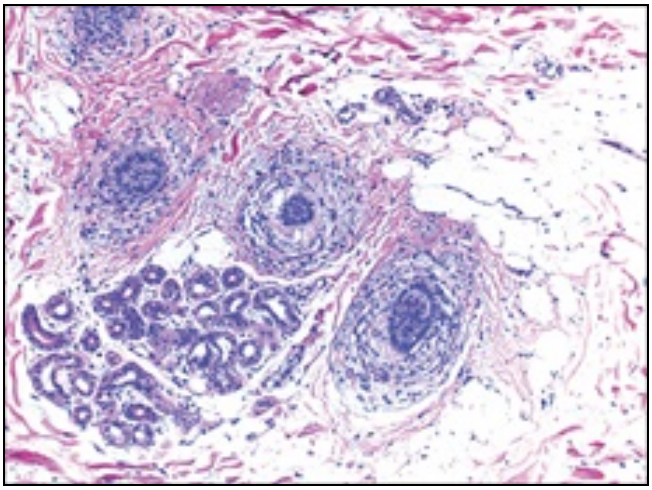

Fig 8: "Swarm of vbees" pattern of lymphocytes surrounding the hair follicle [11]

Pathophysiology

It is presently unidentified precise pathophysiology of the disease. Evidence indicates AA is result of an autoimmune response to HFs are affected by both environmental and genetic factors [12].

Genetic factors

AA and familial history exhibit a high correlation (10%-42%) in observational studies. Genome-wide association studies have linked AA to a plethora of single-nucleotide polymorphisms. The most significant risk factor for AA, Human leukocyte antigen-DR is located on chromosome 6 according to a recent meta-analysis. These HLA class II alleles are closely associated with CD8+ T-cells and CD4+, which are essential effector cells in AA. BCL2-like protein 11, also known as BIM, is responsible for the regulation of autophagy during the development of disease, and it was also included in this investigation. In addition, the susceptibility to AA can be influenced by genes that encode for natural killer cell receptor D ligands and are downstream effectors of the JAK pathway. Apoptosis, autophagy, and T-regulatory cells (Tregs) are additional pathways that are implicated; however, additional information is required to ascertain the precise mechanisms [13, 14].

Environmental factors

The likelihood of environmental factors either exacerbating or increasing AA is considerable. However, the literature from human studies is ambiguous, despite the frequent reference to stress as a contributing factor to AA. In a mouse model, peripheral and central hypothalamus pituitary adrenal axis demonstrated increased activity in contrast to that of normal rodents. elevated adrenocorticotropic hormone, corticosterone, and estradiol correlated to elevated pro-inflammatory cytokine levels in the skin, suggesting a potential role of psychological and physiological stressors to cause AA. Although their precise effects are unknown, infections, vaccinations, hormone fluctuations, and diet are additional potential environmental stressors which related to AA. New research has underscored correlation between AA and Vitamins D and A levels, and soy products have been linked to AA in the mouse model. It is probable that a wide range of environmental factors contribute to disease progression [15].

Immune privilege zone

Downregulation of MHC I and presence of β2 macroglobulin molecules in natural hair follicle (HF) are reasons for existence of IP zone. transforming growth factor-β and α-melanocyte-stimulating hormone, which are immunosuppressant molecules, are produced, and the activity of antigen-presenting cells is reduced. However, it is hypothesized that an unknown autoantigen has compromised the IP zone in AA. The infiltration of CD4+, CD8+, and other inflammatory cells into the IP zone can be induced by interferon-γ and interleukin (IL)-2. HL may be the consequence of all of these modifications, which manifest as inflammation of the HF [16].

Diagnosis

Based on cases had medical history and physical examination, t AA diagnosis is generally straightforward. Skin biopsies are typically diagnostic for patients whose diagnoses are ambiguous. HL acuity in biopsy location influences histopathological characteristics of AA. A peribulbar, dense, lymphocytic infiltrate that surrounds anagen HFs is characteristic of an acute disease. This infiltrate has been likened to a "swarm of bees" pattern. Characteristics of subacute disease contain an increase in catagen and telogen hairs and a decrease in anagen hairs. Conversely, chronic diseases are distinguished by diminished terminal hair and increased miniaturized hair, as well as varying degrees of less pronounced inflammation. A histopathological examination of 50 AA patients revealed microscopic abnormalities in 66% of the samples obtained from perilesional, clinically unaffected scalps in one study. Histopathological sampling of non-affected scalps is not yet established as a method for evaluating the spread of AA and managing it. Trichotillomania, aplasia cutis, tinea capitis, secondary syphilis, temporal triangular alopecia,and traction alopecia are significant conditions that may serve as differential diagnoses for AA [4].

Severity staging

Historically, AA has been classified as patchy AU, AT, AA, diffuse AA, and ophiasis based on HL pattern. Historically, AA has been classified as patchy AU, AA, AT, diffuse AA, and ophiasis based on HL pattern. Numerous instruments have been created to simplify assessment of scalp severity of AA in clinical practice and trials [17].

Severity of alopecia tool (SALT) scoring

To evaluate AA severity and monitor response to treatment, SALT scoring procedure is most frequently employed tool in clinical trials and practice. First projected by Olsen *et al.* [18] in 2004, cranium is divided into 4 affected regions by SALT score: back (24%), top (40%), right and left sides (18% each), and center (18%). A full crop of hair is represented by a score of 0, while a score of 100

corresponds to complete hair loss. SALT score is a straightforward and efficient assessment to administer in practical situations. However, SALT score doesn't account for non-scalp factors that may influence disease severity, like psychosocial morbidity or facial hair involvement, despite its pervasive use. Consequently, the SALT score is rendered less beneficial when HL is subtle. Olsen *et al*. [19] In 2016, the SALT II visual aid was subsequently proposed, This allows the assessor to more precisely identify concomitant areas of non-AA hair loss and more delicately divvy up the assessment of scalp hair loss.

Alopecia areata investigator global assessment (AA-IGA™) Scale

SALT score is employed by AA Investigator Global Assessment (AA-IGA™) Scale to indicate the severity of the disease, with individual SALT ranges. There are 5 clinically meaningful graduations of scalp HL, as defined by perspectives of patients and clinicians. Disease severity is determined by scalp HL percentage, which is classified as (95-100%) very severe, (50-94%) severe, (21-49%) moderate, (1-20%) limited, and (0%) none. AA-IGA does not account for psychosocial burden or non-scalp-related hair loss, as does SALT score. Moreover, AA-IGA's ranges aren't universally recognized by all dermatologists [20].

Alopecia density and extent (ALODEX) score

ALODEX score is a method that incorporates HL density and extent to determine the ultimate percentage of hair loss. Although manual calculation is feasible, it is most efficiently executed through an iPad application that is predicated on the SALT II visual assistance [21].

Alopecia areata progression index (AAPI)

AAPI was established by Jang *et al*. [22] within 2016. As SALT score calculation, cranium is also alienated to 4 quadrants. However, trichoscopic findings and a hair pull test are used to assess activity of AA disease, in addition to percentage scalp hair loss. This scoring instrument does not consider psychosocial burden or non-scalp-related hair loss.

Alopecia areata severity index (AASI)

A relatively new instrument, AASI was introduced by Majid *et al*. [23]. It evaluates the cranium, upper face, and beard for HL on an individual basis to produce a total severity score (i.e., AASI = AASIbeard + AASIupper face + AASIscalp). utmost AASI score for males is 250, while for females it is 150. Nevertheless, Additional validation is required, as it has only been assessed on a singular population group.

Alopecia areata scale

Following a recent academic-industry collaboration among 22 dermatologists with experience in the administration of AA, the AA Scale was recently proposed. Severity of AA is classified as mild ≤20%), severe (50-100%), or moderate (21-49%) according to the extent of scalp hair loss. If any of the following are present, the severity ratings of AA are elevated by one level in cases with mild or moderate disease:

1. The adverse effects of AA on psychosocial functioning.
2. Prominent eyebrows or eyelashes.
3. Inadequate response following a minimum of six months of treatment.
4. A positive hair draw test that is diffuse (multifocal) and that is consistent with speedily progressive AA [24].

Non-scalp measures of AA severity

For clinical trials, distinct measures of non-scalp severity of AA have been devised, including Patient-Reported Outcome eyelash, C and linician-Reported Outcome nail assessment metrics, and Eyebrow. Stefanis *et al*. [17] In the year 2021, a new scoring system was implemented to determine the degree of beard HL in AA: Alopecia Barbae Severity score. Nevertheless, additional verification is necessary. Assessing psychosocial burden

Although most AA severity assessment instruments do not include psychosocial burden, Separate evaluations have been conducted using Depression Scale and,Hospital Anxiety Perceived Stress Scale, and Dermatology Life Quality Index [21].

Management

Dermatologists exhibit significant variation in their approaches to treating AA. Several expert consensus statements and guidelines have been planned to simplify diseases management. psychosocial disease burden of a patient must be considered in context of holistic management. The development of numerous novel targeted treatment strategies has been facilitated by recent advancements in the aetiopathogenesis of AA [25].

Conservative measures

Observation and reassurance may be sufficient management for certain patients with acute and limited AA, as up to 80% of them may experience spontaneous remission. Wigs, hair extensions, color-matched wool fibers, and top pieces are additional camouflage techniques that have been successfully employed [1].

Topical therapy

In cases of limited to moderate disease, topical treatment may also be considered to expedite hair regrowth. Minoxidil, corticosteroids, and immunotherapy comprise topical treatments. Guidelines from Japanese Dermatological Association (JDA) and British Association of Dermatologists have outlined a variety of strategies for AA management, as well as an Australian expert agreement statement [25].

Topical corticosteroids

Neonatals and adults who are incapable of tolerating intralesional corticosteroids are typically administered potent topical corticosteroids as their initial treatment. In addition to expediting the recuperation of damaged HFs, it is hypothesized that they can mitigate and contain inflammation in AA lesions. Efficacy reports are inconsistent, despite their ubiquitous use. Long-term use is generally discouraged; however, skin atrophy is seldom observed, despite concerns. [1].

Topical immunotherapy

Since 1976, topical immunotherapy has been employed to manage AA. It is hypothesized that immunotherapeutic agents, including diphenylcyclopropenone and squaric acid dibutyl ester, function by inducing antigenic competition, which prevents CD4+ T cells from assaulting HFs. It has been reported that patchy AA has a high response rate (88-100%); however, this rate is significantly lower in severe

AA (60%) and AT/AU (17%). For those of all ages who have moderate to severe AA, the JDA guidelines suggest topical immunotherapy. In case of extensive disease, ophiasis pattern AA, and minors, topical immunotherapy is recommended as either a second-line or first-line therapy according to Australian expert consensus guidelines. Blisters, urticaria, and depigmentation are potential adverse effects of treatment, which can be time-consuming [25].

Dithranol

In patients with limited or extensive disease, topical dithranol is an additional second-line treatment option. Treatment objective is to produce a low-grade, irritant dermatitis. Topical dithranol seems to be somewhat less efficacious than intralesional corticosteroids and topical immunotherapy, despite some efficacy reports. Additionally, epidermis may experience irritation and staining, which can be problematic adverse effects [26].

Topical minoxidil

A dose response effect is observed in minoxidil, a hair growth promoter that has been employed to treat a variety of HL disorders, like androgenetic alopecia. In cases of limited AA, cosmetically acceptable regrowth has been observed; Nevertheless, it is cosmetically ineffective in AU and AT settings. An adjunctive treatment, topical minoxidil should be administered when appropriate. Facial hypertrichosis and dermatitis are potential adverse effects of medication, despite its generally favorable tolerability [1].

Intralesional corticosteroids

Adults with isolated AA regions (<50% scalp involvement) are routinely treated with intralesional corticosteroids, including long-acting triamcinolone acetonide, which are recommended as a first-line therapy in guidelines of JDA and Australian expert consensus statement. Triamcinolone is habitually combined with normal saline or lignocaine. The cranium is treated with a concentration of 5mg/mL, while the eyebrows, face, and beard are treated with 2.5mg/mL. Until regrowth is observed, injections are administered every 4-6 weeks. If no regrowth is observed, injections are discontinued at 6 months. Typically, intralesional corticosteroids produce superior outcomes compared to topical corticosteroids; Nevertheless, those under the age of ten may find them less suitable. Particularly in darker phototypes, hypopigmentation and skin atrophy are potential hazards [25].

Systemic corticosteroids

For AA and refractory cases, oral corticosteroids may be prescribed to halt the rapid progression and extensive hair loss. In spite of the fact that therapy is frequently effective in up to 80% of patients, AA relapse may occur in 50% of responders after dose reduction or treatment discontinuation. There are numerous administrative strategies that may be implemented. prednisolone initial dose might be high (0.5-0.75mg/kg) and gradually tapered over a period of 6 to12 weeks. Alternatively, cases started and continued a static dose (0.25mg/kg) for 6 to12 weeks or started on a lesser dose (0.1-0.2mg/kg) that is up-titrated in accordance with tolerability and response. Pulse therapy may also involve the administration of oral corticosteroids. The duration of treatment is restricted by the potential hazards associated with prolonged oral corticosteroid use. Australian expert consensus statement guidelines recommend cases had corticosteroid responsive however also corticosteroid dependent transition to a steroid-sparing agent. This sentiment is echoed by the JDA guidelines, which suggest that oral corticosteroid use be restricted to adults with rapidly progressive AA and a scalp involvement of ≥25%. Intravenous (IV) or intramuscular (IM) administration of long-acting corticosteroids is an alternative to oral consumption. There is a suggestion that the side effect profile of IM and IV delivery may be preferable to that of oral delivery. IV pulse therapy is a treatment option for individuals with severe and acute AA, as indicated by JDA guidelines, and it is widely utilized in Japan. Nevertheless, it isn't frequently employed in North America, Europe, or Australia [25].

Steroid-sparing agents

This is a challenging endeavor to manage chronic and recalcitrant AA. medicines like azathioprine, cyclosporine, and methotrexate have been used as monotherapy or in mixture with oral corticosteroids to treat severe AA. In chronic AA treatment, methotrexate is a disease-modifying antirheumatic drug (DMARD) that has exhibited reasonable efficacy. Methotrexate can be administered as monotherapy; however, a higher complete response rate is achieved when combined with oral corticosteroids. Additionally, adults seem to be more receptive to treatment than infants. The usual starting dose for treatment is 5-10mg once a week, which is progressively increased every 4-6 weeks in accordance with the patient's response and tolerability (maximum dose: 20-30mg/week). Regrettably, the recurrence of AA is a common consequence of methotrexate cessation. Additionally, the potential side effects and toxicities of methotrexate necessitate close monitoring; it is believed that the risks can be mitigated by concurrently administering folic acid supplements. DMARDs, such as azathioprine, have been implemented to promote hair growth in patients with moderate to severe AA. It is typically administered at a moderate dose (0.5-1mg/kg/day) and progressively increased each 4-6 weeks in accordance with tolerability and response to reduce the likelihood of gastrointestinal distress (maximum dose: 2-3mg/kg/day). An inhibitor of calcineurin, cyclosporine, has been implemented to promote hair regrowth in AA. The initial dose is typically 2mg/kg per day, administered in three divided doses. The maximum dose is 5mg/kg, and on the basis of response and tolerability, the dose is incrementally increased every 4-6 weeks. Cyclosporine possesses severe potential risks that are exacerbated by the duration of treatment, such as hepatotoxicity, nephrotoxicity, and gastrointestinal distress [1].

Platelet-rich plasma (PRP)

Through its anti-inflammatory properties, PRP is a novel therapeutic approach that has been shown to stimulate regeneration in AA-affected regions. A concentrated form of PRP protein is produced by centrifuging whole blood to remove red blood cells. There is a need for additional research to verify its effectiveness [25].

Other systemic agents

In small and uncontrolled retrospective case series and case reports, numerous additional systemic agents have been identified. The treatment regimen comprises dapsone,

psoralen ezetimibe simvastatin, oral minoxidil, sulfasalazine, and mycophenolate mofetil, in addition to ultraviolet A. photochemotherapy [27].

Emerging therapeutic approaches

Biologics

Numerous biologics that target Th1 and Th2 cytokines have been evaluated for the treatment of AA. AA in patients with concomitant AD has been successfully managed by dupilumab, an IL 4Rα blocker that inhibits both IL 4 and IL 13. Nevertheless, the use of dupilumab has also been associated with new AA development and pre-existing AA exacerbation. Tildrakizumab, a high affinity monoclonal antibody that targets IL 23, was of minimal benefit to patients with chronic AA. In same vein, ustekinumab, a monoclonal antibody that was designed to target IL 12/IL 23p40, elicited conflicting results, as it both ameliorated and exacerbated the condition. Additionally, multiple IL 17 inhibitors, including secukinumab, ixekizumab, and brodalumab, have yet to demonstrate any to minimal benefit in the treatment of AA, despite proposed significance of the Th17/IL 17 axis in the pathogenesis of AA. In spite of prevailing theory that elucidates AA pathogenesis, TNF α inhibitors etanercept and adalimumab have been demonstrated to be ineffective treatments [28].

Janus kinase (JAK) inhibitors

A potentially effective new therapy for moderate to severe AA is JAK inhibitors. JAK3, JAK2, JAK1, and TYK2 are four intracellular enzymes that are part of JAK family and have roles in defense, hematopoiesis, and the immunological response. SLE, Alzheimer's disease, rheumatoid arthritis, psoriasis, and inflammatory bowel disease are among the immune-mediated conditions that have been treated with pharmacologic suppression of JAK enzyme family. It has been demonstrated that certain JAK inhibitors are useful in AA treatment [29].

Tofacitinib, a JAK 1/3 inhibitor, has been publicised to be effective in treatment of adult and pediatric AA in numerous studies. After six months, AA patients who were administered facitinib 5mg twice daily exhibited a mean reduction in SALT score of 95.2%, as demonstrated by Almutairi *et al*. in an open-label study. Moreover, the mean reduction in SALT score was 93.8% in cases that were administered ruxolitinib (20mg twice daily), a selective JAK 1/2 inhibitor, after six months. The treatment of severe AA with baricitinib, a selective and reversible JAK 1/2 inhibitor, has been found to be effective in a phase II study of 110 adults. Compared to the placebo group (3.6%), the proportion of patients who achieved a SALT score of ≤20 was substantially higher in the baricitinib 2mg (33.3%) and 4mg (51.9%) groups at week 36. In phase II clinical trials, brepocitinib, a selective JAK 1 /TYK 2inhibitor, and ritlecitinib, a dual TEC/JAK3 inhibitor, have recently been publicised to be effective in the treatment of AA. The most frequent adverse events related to JAK inhibitors use are infection, vertigo, transaminitis, lipid panel derangements, and elevated CK, despite the fact that they are generally well tolerated.Venous thromboembolic events have been documented, despite their rarity. In the same vein, JAK inhibitors have been observed to higher malignancy risk; however, this risk is comparable to that of DMARDs [30].

Hair cortisol

The literature on epidemiological and clinical research has extensively documented the correlation between psychosocial stress and AA. Although stress contributes to prognosis and pathogenesis, the psychobiological processes through which it does so remain enigmatic. It has been postulated that the hypothalamic-pituitary-adrenal (HPA) axis dysregulation is responsible for the adverse physiological effects of stress on the epidermis and hair. Previously, the HPA-axis function has been assessed by assessing cortisol levels in blood, sputum, or urine. Contrary to conventional specimens, the concentration of cortisol secreted into hair has been identified as a novel biomarker of long-term HPA-axis activity, providing a broader array of benefits [31].

Consequences of chronic cortisol excess

Chronic cortisol excess has detrimental effects on both brain and, body which are particularly pertinent to development and AA progression. Insulin resistance, hyperlipidemia, hyperglycemia, abdominal adiposity, and hypertension (HBP) are among adverse effects of chronic cortisol overproduction. In summary, plasma lipoprotein metabolism can be influenced by increased glucocorticoid secretion, which can lead to elevated levels of triglycerides and cholesterol. In addition to contributing to insulin resistance and hyperglycemia, cortisol also activates gluconeogenesis in the liver and opposes the action of insulin. The adverse effects of elevated glucocorticoids on blood pressure and the development of HBP are well-documented. Inhibition of vasodilator hormones, mineralocorticoid-induced sodium retention, and plasma volume expansion are potential mechanisms for the development of cortisol-induced HBP. Additionally, adipocytes development and 11β-hydroxysteroid dehydrogenase I activity in adipocytes are both influenced by increased glucocorticoid output, which can increase the risk of abdominal obesity and visceral adiposity. Subsequently, adipose cells release hormones and metabolites that have a detrimental impact on insulin resistance, plasma lipoproteins, coagulation, and blood pressure [32].

In addition to its systemic effects on cardiometabolic markers, cortisol has a direct impact on the heart and blood vessels. Glucocorticoids are involved in inflammatory modulation, proliferative, and remodelling responses to hurt and vascular occlusion, also,in vascular tone maintenance, in circulatory system, which is GR site and MR expression. The adverse cardiovascular consequences of chronic cortisol excess have been persuasively demonstrated in investigations of patients with endogenous hypercortisolism and those who are treated with glucocorticoid therapy. like, individuals with Cushing's syndrome, a condition distinguished by chronic cortisol excess, are estimated to have a fourfold increased cardiovascular disease (CVD) death risk, a higher CVD incidence complication, and a higher cardiometabolic risk factors prevalence (e.g., resistance of insulin, obesity, HBP) than those who are healthy. Similar to this, patients who receive excessive doses of glucocorticoids are at a significantly increased adverse cardiometabolic markers and cardiovascular risk events [32].

Methods for assessing cortisol levels

Measurement of cortisol in blood, urine, and saliva

Measurements of endogenous cortisol levels in body fluids, like blood, saliva, and urine, have been traditional method

of evaluation. At a single time, point, blood samples deliver measurements of the circulating levels of both bioactive (free) cortisol and CBG-bound cortisol. Conversely, urinary cortisol measurements suggest cumulative exposure to bioactive cortisol ranged 12 - 24 hours. Samples of saliva may also be employed to quantify bioactive cortisol levels. However, sublingual cortisol only quantifies the concentration of cortisol at a single time point, like blood samples. In order to develop a comprehensive profile of cortisol secretion, it is necessary to collect multiple saliva or blood samples throughout the day, as cortisol exhibits a distinct diurnal rhythm. Saliva has gained popularity because of its less intrusive nature, as it is difficult to conduct repetitive blood sampling beyond clinical or laboratory settings. For the surveillance of acute HPA-axis responses in acute laboratory stress paradigms, these methods are particularly advantageous. In contrast to information on long-term exposure to elevated cortisol levels, these methodologies are fundamentally defective in that they only provide transient or short-term estimates of cortisol levels [33].

On a situational and interindividual basis, the concentration of cortisol in urine, blood, and saliva is also subject to fluctuation because of a variety of confounding factors, including transient events and moods, circadian rhythm, and study procedures. The selection of days may not be representative, and there are few studies that acquire samples covering a span of multiple days. Excessive participant burden and incomplete sample collection may result from the collection of recurrent cortisol measures over the course of a day. Critically, the aetiology and progression of short-term cortisol reactivity are more likely to be influenced by prolonged and recurrent exposure to increase levels of cortisol. In fact, transient and acute cortisol exposure is generally benign and facilitates successful adaptation to environment. Conversely, persistently raised levels of cortisol are detrimental and linked to poor health [33].

Cortisol in hair

Hair develops in cycles, with intervals of anagen, catagen, and telogen. These periods are characterized by the hair's cessation of growth, which can be effortlessly extracted by tugging. 0.2 mm/day to 1.12 mm/day, or 6 to 33.5 mm/month, is the spectrum of hair growth rates on the scalp. Scalp hair develops at a faster pace than pubic hair, that in turn changes a faster pace than beard hair. Racial and gender factors also influence hair growth rate, as hair growth of Caucasian is quicker than in Asian and hair develops in women's scalp quicker than men's scalp. Additionally, the growth rate of hair slows down with age. The anagen stage is occupied by the greatest number of follicles (85%) in scalp vertex region, where hair grows at quickest rate. Ito and colleagues [34] showed epidermis is an equivalent "peripheral" HPA-like system that is capable of locally managing responses to stress, as confirmed by an original hypothesis. In accordance with the data presented, HF was equipped with a comprehensive HPA-like system that generated ACTH, CRH, and cortisol without a necessary connection to the general blood supply, thereby bypassing the HPA axis.

Ito *et al*. [34] The effects of CRH stimulation on HFs extracted from patients undergoing face-lift surgery were investigated by researchers. In response to ACTH stimulation, HFs produced a greater amount of cortisol, exhibited regulatory feedback like that observed in the central HPA axis, and produced an increased amount of ACTH. Potentially significant were demonstrations that the production of cortisol in hair could be independent of central HPA influences, such as its production in cultured melanocytes and dermal fibroblasts. Hair cortisol was further investigated as a peripheral system that could function independently from central HPA axis, as evidenced by HF development as an independent source of cortisol in those experiments [35, 36].

Conclusion

In conclusion, this review article reinforces the link between chronic stress, HPA axis dysregulation, and AA by demonstrating significantly elevated scalp hair cortisol levels in AA cases than healthy controls. Hair cortisol and SALT scores exhibit a positive correlation, which implies that stress may be a factor in the severity of the disease. These findings suggest that hair cortisol may serve as a biomarker for chronic stress exposure in AA and underscore the potential of stress management in disease prevention and treatment.

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How to Cite This Article
Sorour NE, Abdel Rahman SES, Husseini NFA, Shams GM. Scalp hair cortisol concentration in patients with alopecia areata and correlate its level with the disease variables. International Journal of Dermatology, Venereology and Leprosy Sciences. 2025; 8(2): 105-113.