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Evaluation of Serum G Protein-Coupled Estrogen Receptor 1 (GPER-1) Levels in Patients with Androgenetic Alopecia and Telogen Effluvium

Youmna Ossama Mahmoud Ali Saraya[1], Hanan Ahmed Salem[1], Yousra Ibrahim El-Tantawy Sadeq[2], Sherihan Hassan Allam[1].

1Dermatology, Andrology & STDs, 2 Clinical Pathology Department, Faculty of Medicine - Mansoura University, Egypt

Corresponding author: Youmna Ossama Mahmoud Ali Saraya1, **Email:** yomna.saraya@mans.edu.eg, **Tel:** +201159267772

ABSTRACT

Background: Androgenetic alopecia (AGA) is a non-scarring condition characterized by a gradual reduction in scalp hair density, typically exhibiting a well-defined distribution pattern. G protein-coupled estrogen receptor 1 (GPER-1) participates in rapid estrogen-mediated signaling through the activation of multiple protein kinase cascades.

Objectives: This study aimed to investigate serum GPER-1 concentrations in AGA cases and telogen effluvium (TE), and to assess the potential role of this biomarker in the pathogenesis of both conditions.

Patients and methods: This investigation enrolled a total of 84 participants, stratified into three distinct cohorts: Group A comprised 28 subjects clinically diagnosed with AGA, group B included 28 cases presenting with TE and group C consisted of 28 age- and sex-matched healthy controls. All subjects underwent clinical and dermoscopic examinations, along with hormonal profiling, including measurements of serum dihydroepiandrosterone sulfate, total testosterone, estradiol (E2), and prolactin. Serum GPER-1 levels were quantified using ELISA kit.

Results: A notable negative correlation was identified between GPER-1 and E2 levels. Among the study groups, AGA cohort exhibited the highest mean GPER-1 level, followed by TE group, with the lowest levels observed in the controls. GPER-1 demonstrated a moderate discriminatory capacity in distinguishing healthy controls from cases with either AGA or TE. However, its ability to differentiate between cases with AGA and those with TE was limited.

Conclusion: Estrogen hormone has an important role in hair growth. Serum level of GPER-1 could be used as a biomarker with reasonable degree of accuracy in differentiating AGA from TE and control.

Keywords: Androgenetic alopecia, Serum G protein coupled estrogen receptor 1, Telogen effluvium.

INTRODUCTION

AGA represents the most prevalent form of hair loss in both men and women. In males, the condition—commonly referred to as male pattern hair loss—typically begins during adolescence or by the third decade of life. In contrast, female pattern hair loss exhibits a bimodal age distribution, with incidence peaks occurring in both premenopausal and postmenopausal periods [1]. AGA arises from a multifactorial pathophysiological process. Evidence from twin studies indicates that hereditary factors contribute to nearly 80% of risk associated with development of baldness [2]. Accumulating evidence indicates that AGA arises from response of hair follicle cells to androgens in individuals with an underlying genetic susceptibility. Testosterone is metabolized into DHT which has more affinity to androgen receptor. This leads to secretion of many cytokines by hair follicles, such as TGFβ 1, IL-1α , and TNFα, which leads to premature termination of anagen phase [3]. Emerging evidence also indicates that AGA is linked to dysregulated expression of inflammatory cytokines, with chronic microinflammation acting as a contributory factor in disease progression [4]. Environmental and lifestyle factors are also implicated in pathogenesis of AGA, primarily through their contribution to oxidative stress, which adversely affects hair follicles both during and following hair production [5]. TE is one of the most common causes of diffuse hair loss disorders also affecting both males and females. The relationship between TE and age remains inconclusive. However, it is well recognized that elderly women exhibit increased susceptibility to acute forms of TE [6]. TE may manifest as either acute or chronic hair shedding, often accompanied by a range of clinical symptoms, including trichodynia. Although its exact pathophysiology remains poorly understood, disruptions in normal hair cycle have been proposed as a potential underlying mechanism [7]. Numerous factors can initiate a disturbance in hair cycle including physiologic or emotional stresses, nutritional deficiencies, endocrine imbalances and multiple drugs [8].

The physiological effects of estrogenic compounds on target tissues are mediated through specific estrogen receptors, primarily GPER, ERα, and ERβ. These receptors are expressed in a variety of tissues, including skin and cells of scalp [9]. Several studies have investigated distribution of estrogen receptors α and β in scalp, as well as gender-related differences in their expression. However, data regarding influence of estrogen on hair follicles through GPER remain limited [10]. GPER1 functions as an active estrogen receptor, orchestrating estrogen-dependent signaling across various physiological systems, including nervous, reproductive, metabolic, cardiovascular, and immune systems [11]. GPER1 is expressed in a variety of immune cells, including T cells, B cells, mononuclear cells, macrophages, and neutrophils [12]. It also has a proven inhibitory and promoting effects on various tumors and systemic diseases [13].

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PATIENTS AND METHODS

Study design: This cross-sectional, case-control investigation was conducted at Outpatient Clinic of Dermatology, Andrology, and STDs Department, Mansoura University Hospitals, Mansoura, Egypt. A total of 84 participants were enrolled and stratified into three groups: Group A comprised 28 cases diagnosed with AGA, Group B included 28 individuals with TE, and Group C consisted of 28 healthy controls matched for age and sex. **Eligibility criteria:** The present study encompassed both male and female participants diagnosed with either AGA or TE, representing various clinical variants and degrees of severity.

Clinical confirmation of PHL diagnosis was obtained based on the following factors: A negative hair pull test, slow development of hair loss at fronto-vertical site, visual confirmation of short, thin hairs present in vertex, and confirmation by dermoscopic examination: More miniaturised thin vellus hairs, particularly in frontoparietal region, and a greater preponderance of single hair pilosebaceous units in frontal area as opposed to occipital area are associated with a shift in hair shaft diameter diversity of more than 20% [14].

Exclusion criteria: Cases with other dermatological diseases, cases with other scalp or hair shaft disorders e.g., alopecia areata, scarring alopecia, Pregnancy and lactation, cases with endocrine disorders (dysregulated thyroid functions and diabetes mellitus) or known systemic disorders and cases taking hormonal therapy.

Methods: All participants underwent comprehensive history taking, which encompassed age, sex, disease duration, smoking status, comorbid conditions, past medical history, and current treatments. Additionally, each subject received a thorough general and dermatological examination. Local scalp examination was conducted to exclude cases with any signs of inflammation or scarring. Trichoscopic examination was performed with a handheld dermoscope attached to a smart phone camera with least 3-4 images taken for each case. The severity of disease was assessed using Hamilton-Norwood scale, which serves as a valuable tool for classifying male pattern hair loss (Figure 1). This scale categorizes clinical presentations into seven distinct stages and provides a visual representation of progressive patterns of balding [15].

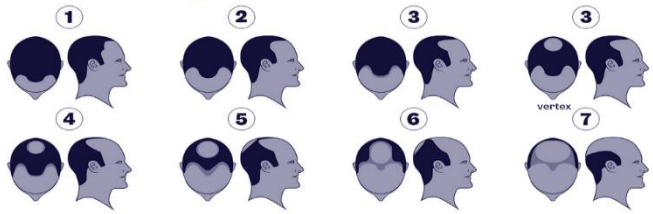

Figure (1): Hamilton-Norwood scale [15].

FPHL severity was evaluated using Ludwig scale (Figure 2), which classifies degree of hair density reduction over crown region into three distinct clinical grades [16]. Hair pull test was done for confirmation and assessment of TE cases [17].

Figure (2): Ludwig scale for female hair loss: stage I, stage II, and stage III [16].

Hormonal profile assessment was conducted in form of serum dihydroepiandrosterone sulphate, total testosterone, E2 and prolactin. Serum levels of GPER-1 were measured using Human GPER-1 ELISA Kit (Catalog No: E4779Hu; BT LAB, Bioassay Technology Report, Zhejiang, China). This assay is based on ELISA technique.

Ethical consideration: The whole study design was approved by The Local Ethics Committee, Faculty of Medicine, Mansoura University. Written informed consents were obtained from all participants before inclusion in the study. Prior to enrollment, the study objectives and procedural details were thoroughly communicated to all participants. Confidentiality and personal privacy were upheld at every stage of the research. All participants were informed of their right to voluntarily withdraw from the study at any stage without incurring any consequences. Data collected were strictly employed for the objectives of the current research. The study protocol adhered fully to ethical principles established in Declaration of Helsinki.

Statistical analysis

Data were revised, coded, and analyzed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics included mean ± SD, median and range for numerical data, and frequency with percentage for categorical data. For analytical statistics, Mann–Whitney U test was used to compare non-parametric variables between two groups, while one-way ANOVA assessed differences in parametric variables across more than two groups. Kruskal–Wallis test was applied for non-parametric comparisons among multiple groups. Associations between categorical variables were evaluated using Chi-square test, with Fisher's exact or Monte Carlo tests applied when expected cell counts were less than 5 in more than 20% of cells. Spearman's correlation was used to assess relationships between quantitative variables. ROC curve analysis evaluated sensitivity and specificity of quantitative diagnostic measures, with optimal cut-off point defined by highest AUC. AUC values > 0.9 indicated high accuracy, 0.7–0.9 moderate accuracy, 0.5–0.7 low accuracy, and 0.5 denoted no diagnostic value. Statistical significance was defined as a p-value ≤ 0.05 at a 95% CI.

RESULTS

The male to female ratio in all groups were: 46.4% (AGA), 42.9% (TE) and 50.0% (Control) with no substantial variations observed between groups ($p > 0.05$). AGA group exhibited highest mean age (30.68 ± 8.94 years), followed by controls (29.00 ± 6.71 years) and TE group (27.07 ± 7.78 years). Nevertheless, this variation did not attain statistical significance ($p > 0.05$) (**Table 1).**

Table (1): Comparison between the three studied groups regarding general characters

	AGA (n = 28)		Telogen effluvium (n = 28)		Control (n = 28)		Test	P1
	No.	%	No.	%	No.	%		
Sex								
Male	13	46.4	12	42.9	14	50.0	X^2= 0.287	0.866
Female	15	53.6	16	57.1	14	50.0		
Age (years)								
Mean ± SD.	30.68 ± 8.94		27.07 ± 7.78		29.0 ± 6.71		F= 1.475	0.235
Median	29.0		25.0		29.50			
Min. – Max.	17.0 – 53.0		17.0 – 45.0		20.0 – 47.0			
Marital status								
Single	18	64.3	15	53.6	9	32.1	X^2= 8.707	MC 0.169
Married	9	32.1	13	46.4	19	67.9		
Divorced	1	3.6	0	0.0	0	0.0		

SD.: Standard deviation, Min.: Minimum, Max.: Maximum, X2: Chi Square, MC: Monte Carlo, F: One Way ANOVA test, p1: Comparing the three studied groups, p2: Comparing AGA and telogen effluvium, p3: Comparing AGA and control, p4: Comparing telogen effluvium and control, *: Significant p value <0.05.

The mean duration for AGA was 69.43 ± 51.05 months, significantly longer than mean duration for TE at 22.68 ± 53.11 months ($p < 0.001$). The median duration for AGA was 54.0 months, while it was 6.0 months for TE. The results indicated that duration of AGA tends to be longer compared to TE (**Table 2).**

Table (2): Comparison between AGA and telogen effluvium regarding duration.

		AGA (n = 28)	Telogen effluvium (n = 28)	Test	p
Duration (months)	Mean ± SD.	69.43 ± 51.05	22.68 ± 53.11	U= 84.0*	<0.001*
	Median	54.0	6.0		
	Min. – Max.	12.0 – 240.0	1.0 – 276.0		

Min.: Minimum, **Max.:** Maximum, **SD:** Standard deviation, U: Mann Whiteny. **P:** Comparing the two studied groups, ***:** Significant p value <0.05.

No significant differences were observed in levels of DHEA-s, testosterone, or prolactin. In contrast, E2 levels showed a statistically significant variation, with AGA group displaying a lower mean value (74.26 pg/mL) compared to TE group (98.05 pg/mL) and controls (89.35 pg/mL) ($p = 0.008$) (**Table 3).**

Table (3): Comparison between the three studied groups regarding serum hormones

	AGA n = 28	Telogen effluvium n = 28	Control n = 28	Test	P1	Pairwise
DHEA s (ug/mL)						
Mean ± SD.	3.06 ± 0.23	3.31 ± 0.28	3.59 ± 0.13	H= 3.420	0.181	–
E2 (pg/mL)						
Mean ± SD.	74.26 ± 8.46	98.05 ± 8.71	89.35 ± 6.80	H = 9.645*	0.008*	p2=0.009* p3=0.006* p4=0.895
Testosterone (ng/mL)						
Mean ± SD.	4.38 ± 1.79	2.78 ± 0.33	2.55 ± 0.60	H = 0.180	0.914	–
Prolactin (ng/mL)						
Mean ± SD.	4.19 ± 1.45	5.15 ± 1.41	3.39 ± 0.80	H = 0.137	0.934	–

SD.: Standard deviation, H: Kruskal Wallis test, Min.: Minimum, Max.: Maximum, p1: Comparing the three studied groups, p2: Comparing AGA and telogen effluvium, p3: Comparing AGA and control, p4: Comparing telogen effluvium and control, *: Significant p value <0.05.

The mean GPER-1 level was highest in AGA group (12.83 ± 10.84 ng/mL), followed by TE group (8.83 ± 6.64 ng/mL) and controls (5.42 ± 1.72 ng/mL). The statistical test revealed a significant difference among the three groups ($p < 0.001$). Pairwise comparisons showed a substantial variation between AGA and TE ($p = 0.046$), AGA and control ($p < 0.001$), and TE and control ($p = 0.008$) **(Table 4).**

Table (4): Comparison between the three studied groups regarding GPER-1

	AGA n = 28	Telogen effluvium n = 28	Control n = 28	Test	P1	Pairwise
GPER-1 (ng/mL)						
Mean ± SD.	12.83 ± 1.84	8.83 ± 2.64	5.42 ± 1.72	H= 15.223*	<0.001*	p2=0.046* p3<0.001* p4=0.008*

Min.: Minimum, Max.: Maximum, SD: Standard deviation, H: Kruskal Wallis test, p1: Comparing the three studied groups, p2: Comparing AGA and telogen effluvium, p3: Comparing AGA and control, p4: Comparing telogen effluvium and control, *: Significant p value <0.05.

A significant positive correlation was observed between GPER-1 and disease duration ($p = 0.016$), while a significant negative correlation was noted between GPER-1 and E2 levels ($p = 0.030$). No significant associations were found between GPER-1 and age, BMI, DHEA-s and testosterone, or prolactin levels (**Table 5).**

Table (5): Correlation between GPER-1 and different parameters among cases with AGA

	GPER-1	
	Correlation Coefficient	**p**
Age	0.295	0.127
Duration	0.450*	0.016*
BMI	0.065	0.744
DHEA s	0.204	0.299
E2	-0.411*	0.030*
Testosterone	0.051	0.798
Prolactin	0.097	0.622

r: Spearman's rho, *: Significant p value <0.05.

No substantial associations were detected between GPER-1 and age, disease duration, BMI, DHEA-s, E2 and testosterone, or prolactin levels (**Table 6).**

Table (6): Correlation between GPER-1 and different parameters among cases with telogen effluvium

	GPER-1	
	Correlation Coefficient	**p**
Age	0.337	0.079
Duration	0.331	0.085
BMI	0.068	0.729
DHEA s	-0.041	0.838
E2	0.165	0.402
Testosterone	-0.230	0.238
Prolactin	-0.141	0.474

r: Spearman's rho, *: Significant p value <0.05.

Table (7) presented validity of GPER-1 for discrimination between cases with AGA and controls. The mean AUC was 0.779, indicating a moderate discriminatory ability. The sensitivity and specificity percentages were 71.43% and 75.0% respectively, with a PPV of 74.07% and NPV of 72.41%. The accuracy of GPER-1 test in this discrimination was 73.22%.

Table (7): Validity of GPER-1 for discrimination between cases with AGA and the control group

GPER-1 (ng/mL)								
AUC	**95% CI**	**p**	**Cut off**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**Accuracy (%)**
0.779	0.653–0.904	<0.001*	>6.2	71.43	75.0	74.07	72.41	73.22

CI: Confidence interval, AUC: Area under ROC curve; PPV, positive predictive value; NPV, negative predictive value. *: P value Significant <0.05.

Table (8) presented the validity of GPER-1 for discrimination between cases with TE and control group. The mean AUC was 0.721, indicating a moderate discriminatory ability. The sensitivity and specificity percentages were 67.86% and 78.57% respectively, with a PPV of 76.0% and NPV of 70.97%. The accuracy of GPER-1 test in this discrimination was 73.22%.

Table (8): Validity of GPER-1 for discrimination between cases with telogen effluvium and the control group

GPER-1 (ng/mL)								
AUC	**95% CI**	**p**	**Cut off**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**Accuracy (%)**
0.721	0.586–0.856	0.004*	>6.21	67.86	78.57	76.0	70.97	73.22

CI: Confidence interval, AUC: Area under curve; PPV, positive predictive value; NPV, negative predictive value. *: P value Significant <0.05.

The table presents the validity of GPER-1 for discriminating between cases with AGA and TE. The mean AUC was 0.608, indicating a poor discriminatory ability. The sensitivity and specificity percentages were both 64.29%, with a PPV and NPV of 64.29% each. The accuracy of GPER-1 test in this discrimination was 64.29%.

Table (9): Validity of GPER-1 for discrimination between cases with AGA and telogen effluvium

GPER-1 (ng/mL)								
AUC	**95% CI**	**p**	**Cut off**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**Accuracy (%)**
0.608	0.457–0.760	0.164	>6.98	64.29	64.29	64.29	64.29	64.29

NPV, negative predictive value, CI: Confidence interval, PPV, positive predictive value, AUC: Area under curve *: P value Significant <0.05.

DISCUSSION

This study aimed to assess serum GPER-1 levels in cases with AGA and TE and to explore its potential involvement in pathogenesis of both conditions. It was designed as a case-control study involving 84 participants, categorized into three groups: Group A included 28 individuals diagnosed with AGA, group B comprised 28 cases with TE, and group C consisted of 28 healthy controls matched for age and sex. All subjects were enrolled from Outpatient Clinic of Dermatology, Andrology, and STDs at Mansoura University Hospitals.

Regarding demographics of present study**,** the male to female ratio in all groups were: 46.4% (AGA), 42.9% (TE) and 50.0% (Control) with no substantial variations observed between groups ($p > 0.05$). Mean age was highest in AGA group (30.68 ± 8.94 years), followed by controls (29.0 ± 6.71 years) and TE group (27.07 ± 7.78 years), a higher percentage of participants in AGA group were single with no substantial variation observed between groups regarding sex, age, mean weight, height, or BMI and marital status. This is in same line with **Bains *et al.*** [18] who reported that cases with AGA had highest mean age of 35 ± 11 years, whereas those with TE had a mean age of 32 ± 12 years, compared to 34 ± 12 years among 60 controls.

The present study revealed that the mean duration for AGA was 69.43 ± 51.05 months, which was significantly longer than the mean duration for TE which was 22.68 ± 53.11 months. **Bains *et al.*** [18] found that the mean duration of disease of AGA was 38.5 ± 5.3 and the mean duration of TE was 31 ± 2 months which was longer in AGA which agrees with our results also.

The present study revealed statistically significant difference between AGA and TE cases compared to controls regarding scalp itching and pain. Higher percentage of participants in AGA group reported scalp itching (53.6%) and scalp pain (35.7%) compared to TE (50% & 42.9% respectively) and control (3.6% & 0% respectively) groups, while no significant differences were found between AGA and TE regarding scalp itching and pain or regarding dietary habits. In disagreement with other study that found cases with TE reported more sensitive scalp, more pain, burning, itching and trichodynia than other type of hair loss in their study. Conversely, in cases with AGA, incidence of scalp sensitivity, burning sensations, pain, and trichodynia did not demonstrate a statistically significant increase when compared to individuals affected by other types of alopecia [19].

With respect to trichoscopic findings, the current study observed that prevalence of empty hair follicles—particularly yellow dots—was substantially higher in AGA group, followed by TE group, and lowest among controls. Similarly, follicular units with only one hair in frontal area were more prevalent in AGA group (67.9%), followed by TE (32.1%) and lastly controls (7.1%). While, upright regrowing hairs were significantly more common in TE group (85.7%), than AGA and controls. These results align with observations of **Kasumagic-Halilovic *et al.*** [20] who reported a substantial increase in

number of yellow dots, pilosebaceous units containing a single hair shaft, and perifollicular hyperpigmentation in individuals with AGA. Moreover, the proportion of miniaturized hairs with a diameter less than 0.03 mm was significantly elevated in AGA cases compared to controls, further supporting diagnostic utility of these trichoscopic features.

The present study revealed that among males, grade VII AGA (30.8%) was the most common, followed by grades VI (23.1%) and V (15.4%). While in females, type I and type II were equally prevalent, accounting for 46.7% each. Type III was observed in only one female (6.7%). While, **Öztürk *et al.*** [21] included 20 women diagnosed with stage 2 AGA, along with 20 men diagnosed with stage 2, 3, or 4 AGA in their study population.

The current study revealed no statistically difference between the groups, regarding level of DHEA-s, testosterone, and prolactin. However, E2 levels differed significantly, with AGA group (mean: 74.26 pg/mL) exhibiting lower levels compared to TE group (mean: 98.05 pg/mL) and controls (mean: 89.35 pg/mL). In contrast to findings of Zhang ***et al.*** [22] who reported significantly elevated serum levels of FT and DHT in cases with AGA compared to controls, the present study did not observe such differences. Also, they further noted that serum levels of SHBG, LH, and FSH were comparable between the two groups. Additionally, no substantial variations in serum androgen levels, including FT and DHT, were identified among AGA cases across different grades of hair loss severity.

The phenomenon whereby androgens exert opposing effects on hair growth depending on anatomical location is known as "Androgen paradox." While, androgens stimulate the development of facial and body hair—such as beard and torso hair—in males, they simultaneously suppress hair growth in scalp regions affected by AGA. This site-dependent response is also evident during puberty, prior to this stage, only fine vellus hairs are present in axillary and pubic areas, whereas pubertal rise in androgen levels induces emergence of terminal hairs, characterized by increased thickness, pigmentation, and curliness [23].

Evidence from current study revealed that mean GPER-1 level was highest in AGA group (12.83 ± 10.84 ng/mL), followed by TE group (8.83 ± 6.64 ng/mL) and controls (5.42 ± 1.72 ng/mL) with statistically significant differences. Consistent with the findings of **Öztürk *et al.*** [21] the present study supports that GPER-1 levels are elevated in cases with AGA, with a reported mean of 30.43 ± 3.83 ng/mL in AGA group compared to 14.18 ± 3.61 ng/mL in controls. This suggests a potential role for GPER-1 in disease pathophysiology. Supporting its broader immunological significance, evidence from a murine model of Crohn's disease demonstrated that reduced GPER-1 expression was associated with diminished colonic inflammation. Furthermore, GPER-1 agonists have been shown to exert immunosuppressive effects in Crohn's disease, indicating that GPER-1–targeted therapies may hold promise in maintaining disease remission [24].

The observed associations between GPER-1 and inflammatory processes suggest that elevated GPER-1 levels identified in this study may be linked to perifollicular inflammation characteristic of AGA pathophysiology. Importantly, role of GPER-1 appears to extend beyond estrogen-mediated signaling. Emerging evidence indicates that GPER-1 plays a broader immunomodulatory role, influencing activity of various immune cell types and contributing to regulation of pro-inflammatory pathways **[11].**

The present study revealed significant positive correlation between GPER-1 and duration and a significant negative correlation between GPER-1 and E2, while no significant associations were found between GPER-1 with age, BMI, DHEA, testosterone, prolactin levels, genders and marital status, scalp itching & scalp pain. **Kus *et al.*** [25] reported significantly higher serum GPER-1 levels in cases with AGA relative to controls. They also identified a negative correlation between serum GPER-1 levels and disease duration in both male and female cases. However, their findings did not demonstrate a statistically significant association between GPER-1 and estrogen levels, which contrasts with results of present study. This discrepancy may be attributed to differences in sample size or study design. Moreover, the same study reported a substantial variation in GPER-1 levels between male and female cases with AGA. The elevated GPER-1 levels observed in AGA cases relative to controls, along with significant correlations between GPER-1 concentrations and both disease duration and severity, support notion of an estrogen-independent role for GPER-1 in AGA pathogenesis. Notably, higher GPER-1 levels detected during early stages of AGA—when inflammatory activity is more pronounced—suggest that therapeutic interventions targeting GPER-1 may be particularly effective during this initial phase of the disease.

To best of our knowledge, no more previous studies had investigated role of GPER-1 level in different patterns of hair loss except for two previously studies about its role in AGA, but present study was the first to investigate its role in TE cases. The expression of estrogen receptors α, β, and GPER-1 has been identified in both scalp and skin cells. Several studies have explored distribution of these receptors in scalp, their differential expression based on gender, and their distinct—sometimes opposing—effects on hair follicle biology. Despite these efforts, precise mechanisms through which estrogens influence hair follicle function remain

incompletely understood. Nonetheless, emerging evidence suggests that estrogens may exert their effects, at least in part, through GPER-1–mediated pathways [10].

The current study revealed moderate discriminatory ability between cases with AGA and controls that mean AUC was 0.779. The sensitivity and specificity percentages were 71.43% and 75.0% respectively, with a PPV of 74.07% and NPV of 72.41%. The accuracy of GPER-1 test in this discrimination was 73.22%. Regarding discriminating between cases with TE and controls, the current study revealed that the mean AUC was 0.721 indicating a moderate discriminatory ability. The sensitivity and specificity percentages were 67.86% and 78.57% respectively, with a PPV of 76.0% and an NPV of 70.97%. The accuracy of GPER-1 test in this discrimination was 73.22%. And for discriminating between cases with AGA and TE, the present study showed that the mean AUC was 0.608, indicating a poor discriminatory ability. The sensitivity and specificity percentages were both 64.29%, with a PPV and NPV of 64.29% each. The accuracy of GPER-1 test in this discrimination was 64.29%.

A murine study demonstrated that expression of GPER-1 in melanoma cells enhances immune clearance, and further revealed that use of GPER-1 agonists may offer therapeutic benefits, particularly when combined with immunotherapy [26]. GPER-1 has been implicated in pathological progression of SLE. Evidence from a study investigating the role of GPER-1 in SLE-associated skin inflammation demonstrated that estrogen can exacerbate cutaneous inflammation induced by serum IgG through activation of membrane-bound receptor GPER-1 [27]. Moreover, activation of GPER-1 has been specifically shown to reduce formation of α-haemolysin–mediated skin lesions and production of pro-inflammatory cytokines, while simultaneously enhancing bacterial clearance [28]. GPER-1 is involved in both rapid signal transduction and transcriptional regulation. The identification of selective GPER-1 ligands capable of modulating its activity in in-vitro and preclinical models, along with studies utilizing GPER-1 knockout mice, has provided valuable insights into its diverse functional roles [29]. Although in vitro studies have provided compelling evidence that GPER-1 plays a critical role in mediating endogenous effects of estrogen, in vivo confirmation of these findings remains absent. Nonetheless, recent advancements in genetic tools and the development of selective chemical ligands have greatly facilitated investigations into physiological functions of GPER-1 across various tissues. Elucidating role of GPER-1 in estrogen signal transduction holds promise not only for enhancing therapeutic efficacy of estrogen but also for guiding development of novel interventions aimed at minimizing its potential side effects [30] .

LIMITATIONS: This study had certain limitations, most notably relatively small sample size and the fact that it represents the first investigation of GPER-1 levels in cases with TE. Therefore, larger-scale, multicenter studies are warranted to validate and expand upon these findings. Additionally, a more comprehensive understanding of association between GPER-1 and AGA may be achieved by assessing GPER-1 expression not only in serum but also in tissue samples obtained from affected hairy scalp regions.

CONCLUSION

Estrogen hormone has an important role in hair growth, and hence, their levels have to be monitored simultaneously while treating alopecia. Serum level of G protein coupled estrogen receptor 1 could be used as an invasive biomarker with reasonable degree of accuracy in differentiating AGA from TE and controls.

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