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Original Article

Assessment of the efficacy of topical antiandrogen; spironolactone in patients with androgenetic alopecia by dermoscopy

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Abstract

Background Androgenetic Alopecia (AGA) is a non-scarring alopecia characterized by progressive miniaturization of hair follicles with a distinctive distribution in genetically prone males & females. Topical Spironolactone is commonly used as off-label anti-androgen for managment of AGA.

Objective Assessing role of topical 1% spironolactone on hair thickness & count in patients with AGA using dermoscopy.

Methods 26 patients (16 males and 10 females) with ages ranging from 26 to 59 years with a mean±SD of 42.77±6.62 received topical 1% spironolactone solution to apply on the scalp once daily for at least six months. All patients had positive family history. Dermoscopy was performed on fixed areas on the scalp. Images were taken with a digital camera that was connected to the dermoscope just before starting treatment and after 6 months continuous treatment.

Results Significant increase in total terminal, terminal thick and total hair count in female patients along with a significant increase in total terminal, terminal thin, vellus and total hair count in male ones after treatment with topical 1% spironolactone were seen. However, thin and vellus hair in female and thick hair in male revealed no significant difference post spironolactone treatment.

Conclusion Spironolactone is an effective & harmless treatment in both females & males with AGA.

Key words
Androgenetic alopecia, dermoscopy, antiandrogenic drugs, spironolactone.

Introduction

AGA also known as patterned hair loss in men & women, it is progressive and if left untreated leads to baldness causing considerable anxiety and concern.[1] Despite the prevalence of AGA increases with age, thinning can start with puberty.[2] In AGA, miniaturized, vellus hairs gradually replace the thick terminal hairs in well-defined forms. In males, typical pattern hair loss starts beyond temporal & vertex areas of the scalp. Usually the hairs on sides and back areas

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of scalp are not affected by the disease, giving a characteristic appearance 'Hippocratic wreath'; AGA barely develops into complete baldness. Norwood–Hamilton scale is the most widely used classification, grading male AGA from type I to type VIII.[3] Women present with different pattern than men. There is distinctively diffuse thinning without hairline recession, infrequently causing complete hair loss.[4] Ludwig scale ranks the severity of FPHL and ranging from I to III.[5] Other scales like Sinclair scale and Savin scale may be used.[6,7] In AGA, anagen phase duration is decreased, changing the ratio between anagen: telogen hairs from 12:1 in normal scalp to less than 5:1 in AGA.[8] The shortened anagen phase, and the decrease in size of dermal papilla leads to follicular miniaturization with production of shorter, thinner hairs. Since more follicles undergo miniaturization, scalp hair progressively declines. These changes are usually attributed to genetic and hormonal factors.[9] Puberty in males is associated with obvious elevation in androgen production which cause facial hair growth and thinning of hairs at the temples & scalp vertex, this is known as the 'androgen paradox'.[10] In women, role of androgens is unclear so the term 'female pattern hair loss' may be used in place of AGA.[11] Dihydrotestosterone (DHT) plays a vital role in development of AGA. DHT is a powerful metabolite of testosterone and has a 5 fold higher affinity for androgen receptors (AR).[12] The transformation of testosterone into DHT is arbitrated by 5α-reductase enzyme, this enzyme exists in 2 isoforms in scalp hair follicles. Type II isoform has a major role in DHT production in scalp compared to type I isoform. Males with AGA, there is high expression of type II 5α- reductase in dermal papilla cells with increased DHT concentration.[13] Inheritance of AGA is a complex polygenic trait. The first gene was androgen receptor gene on X chromosome; yet, doesn't clarify the high rate of baldness in affected men. Cytochrome p 450 alpha aromatase enzyme contributes to AGA in females, which participates in estrogen synthesis. Aromatase aids in transformation of testosterone to estradiol, decreasing the intrafollicular testosterone vital for transformation to dihydrotestosterone (DHT). Aromatase enzyme levels are high in the scalp of young females and much higher in frontal hair line compared to male scalp explaining the reduced baldness &relative frontal hair line sparing in FPHL.[1] Other factors include Wnt signaling pathway[4] which is important in regulating telogen-to-anagen transformation & sustaining anagen-phase characteristics in dermal papilla cells via β-catenin pathway.[15,16] These conclusions illustrate that damaged Wnt signaling leads to shortening of anagen phase. Increased prostaglandin D2 synthase at mRNA and protein levels[17] reduce hair growth in human hair follicles and decreased prostaglandin E2 (PGE2) levels in bald scalp, enhance hair growth.[18,19] Multiple treatment modalities for AGA are found, as minoxidil is a widely used treatment for androgenetic alopecia. Its mechanism of action is through affecting hair cycle, which leads to premature termination of the telogen hairs, and prolonging the anagen hairs,[20] 5α-Reductase inhibitors,[21] Prostaglandin analogues,[18,19] antiandrogens,[22,23] supplements, low-level laser therapy,[24,25] Autologous platelet-rich plasma[26] and hair transplantation.[27] Spironolactone is a synthetic steroid structurally allied to aldosterone used for hirsutism treatment.[1] It decreases adrenal androgen production and competitively blocks androgen receptors in tissues. Systemically administered spironolactone is used off-label in FPHL with high safety profile. A substantial proportion of women accomplish partial hair regrowth.[1] Topically applied spironolactone appears to have only a local skin effect with no systemic side effects.[28] The trichoscope is a very useful tool in diagnosing AGA. It is a hair and scalp

dermoscope which allows in vivo visualization of hair shafts, epidermal part of hair follicles, perifollicular epidermis and scalp vessels at high magnification.[29,30] In the present research we aimed to assess the role of topical 1% spironolactone on hair thickness and count in patients with AGA using dermoscopy.

Methods

The study was accepted by the Ethical committee (registration number: 18-026). Contributors have written an informed approval.

This study started with 38 patients with androgenetic alopecia, only 26 patients completed the course of 6 months treatment. Patients (16 males and 10 females) were recruited during the period between December 2018 and March 2020. Eligible patients with no history of treatment for the last 3 months were chosen. Neither topical agents nor any medications were allowed thru the study period. Pregnant and lactating women were omitted from the study. Patients were subjected to full history taking and thorough clinical examination.

During the course of the treatment, special concern was directed to the patient's satisfaction and side effects of spironolactone since female patients were more satisfied and compliant due to minimal side effects, on the other hand male patients were more concerned and less satisfied about side effects e.g. gynecomastia, decreased libido and erectile dysfunction. AGA diagnosis was made clinically and confirmed by dermoscopic examination.

Dermoscopic criteria for diagnosis of AGA (for both male and female patients) were 2 major criteria or 1 major criterion and 2 minor criteria indicating the diagnosis with 98% specificity.[31,32]

Major criteria

1. Yellow dots; >4 in four areas of frontal region.
2. Lower average thickness of hairs in frontal region in comparison to occipital region (50 hairs from each area were examined).
3. More than 10% of fine hairs (<0.03 mm) in frontal region.

Minor criteria

1. Ratio between isolated hairs per follicular unit of the frontal region and occipital region is >2:1.
2. Ratio between the fine hairs in frontal region and occipital region is >1.5:1.
3. Ratio between the peripilar sign follicles in frontal region & occipital region is >3:1. The severity of alopecia was assessed clinically according to adapted Hamilton - Norwood classification scale in male AGA & Sinclair scale in female AGA.

All patients received topical 1% spironolactone solution to apply on the scalp once daily for at least six months. Spironolactone topical lotion was prepared at Pharmaceutical Technology Department by dissolving 1g of spironolactone in 40ml of ethyl alcohol by means of a magnetic stirrer (Wisestir MSH-3OD, Daihan scientific co. Ltd., Korea). This was followed by the gradual addition of 40ml of propylene glycol with continuous stirring. Finally, 20ml of double distilled water was gradually added to yield a solution of concentration 1% (w/v). The prepared lotion was kept in amber colored glass containers and in a cool place till usage. Dermoscopy was performed on fixed areas on the scalp (frontal; 10cm from the glabella, temporal and occipital regions). Trichoscopic examination was done using handheld dermoscope DermLite II Pro at a 10 fold

magnification. 3 images were taken by a digital camera (Canon, Powershot a3300 IS) that was connected to dermoscope on 2 occasions just before starting treatment and after 6 months from continuous treatment. Image of frontal area of each patient before start of treatment was compared to that of the same area after completion of the treatment regarding hair thickness and count. Each subject was inspected by the same dermatologist and trichoscopic valuation was done without awareness of clinical severity. Assessment of trichoscopic pictures was done using ImageJ program, hairs were counted and divided according to hair thickness into terminal hairs (thick; >60 µm and thin; ≤60 µm) and vellus hairs; ≤30 µm in thickness.[31,32]

Statistical analysis

Statistics was carried out using SPSS computer program version 8. Significant difference is done using paired T-test 1 poled hypothesis at $p \leq 0.05$.

Results

The study involved 26 patients with ages ranging from 26 to 59 years with a mean±SD of 42.77±6.62. All patients had positive family history. The adapted Norwood-Hamilton stages of hair loss were identified in male patients as: stage II, 1 contributor; stage III, 4 contributors; stage IV, 2 contributors; stage V, 4 contributors; and stage VI, 4 contributors; stage VII, 1 contributor. The Sinclair scale was detected in female patients as follows: grade II, 3 contributors; grade III, 3 contributors; grade IV, 2 contributors; and grade V, 2 contributors. The disease interval ranged from 2 to 25 years with an average of 7 years. The overall patients' satisfaction was more than 65% (17 out of 26 patients).

During treatment two patients experienced headache, one patient heart burn and three patients scalp itching. Throughout the treatment course no male patient complained of decreased libido or erectile dysfunction by history, and by examination no one developed gynecomastia. Also none of female patients complained of menstrual irregularities. Taking total hair count as an indicator for response, 20 patients showed increase in total hair count, while only 6 patients showed the same or less total hair count than that of the first visit. This indicates that 77% of involved patients responded well to topical 1% spironolactone while 23% of patients showed poor response to topical 1% spironolactone.

Table 1 showed that in a group of 26 patients, 38.5 % females and 61.5 % males are evaluated to establish the role of topical spironolactone via dermoscope on terminal (either thick or thin), vellus and total hair count in patients with AGA.

A paired student T test was done at $p<0.05$, showing significant increase in total terminal, terminal (thick) and total hairs in female patients as well as a significant increase in total terminal, terminal (thin), vellus and total hairs in males after treatment with topical spironolactone. However, terminal thin and vellus hairs in females and terminal thick hairs in males revealed no significant difference after spironolactone treatment.

Total hairs in both sexes significantly increased after usage of spironolactone. Using Pearson's correlation coefficient to estimate if there is a correlation between patients' response to spironolactone treatment and age, gender or duration of AGA, no correlation was found, but there was a positive correlation between response to spironolactone treatment in female patients (not males) and the pretreatment severity degree of the AGA.

Table 1 The effect of treatment with topical spironolactone on thin, thick, vellus, terminal and total hair in patients with androgenic alopecia.

Parameter	*Treatment*	*Min*	*Max*	*Mean±S.D.*	*T value*	*P value*
Terminal (total)	Before	F:74 M:32	F:333 M:324	F:190.82±(70.875) M:203.29±(88.667)	F:3.008	F:0.006*
	After	F:101 M:58	F:359 M:362	F:230±(74.107) M:228.57±(87.047)	M:2.295	M:0.019*
Thick (terminal)	Before	F:13 M:18	F:223 M:230	F:109±(67.721) M:126.357±(72.626)	F:2.326	F:0.021*
	After	F:30 M:20	F:250 M:254	F:143.273±(70.912) M:130.214±(72.922)	M:0.282	M:0.39
Thin (terminal)	Before	F:20 M:14	F:246 M:145	F:8.73±(60.522) M:76.929±(38.557)	F:0.46	F:0.33
	After	F:25 M:32	F:189 M:179	F:90.769±(47.783) M:99.786±(39.294)	M:2.84	M:0.006*
Vellus	Before	F:14 M:14	F:68 M:71	F:30.636±(13.673) M:37.929±(16.825)	F:1.28	F:0.115
	After	F:17 M:25	F:74 M:111	F:39.909±(15.06) M:58±(30.77)	M:2.29	M:0.0195*
Total	Before	F:109 M:91	F:401 M:383	F:221.1±(78.02) M:241.93±(90.08)	F:2.838	F:0.009*
	After	F:170 M:125	F:405 M:408	F:269.818±(76.043) M:287.286± (88.48)	M:3.127	M:0.004*

F: female, M: male, N: number, S.D.: Standard deviation, * there is a significant difference by using paired T-test 1 poled hypothesis at $p<0.05$. Data are expressed as Mean±S.D. Statistics is done using SPSS computer program version 22. Significant difference is done using paired T- test at $p<0.05$.

Discussion

AGA yields a chronic, progressive, patterned hair loss. Androgens, especially, dihydrotestosterone (DHT) bind to androgen receptors in sensitized hair follicles. Polymorphism of androgen receptor gene is sturdily linked to AGA in males but not in females. Most of body hair growth is arbitrated by dihydrotestosterone (DHT), a powerful metabolite of testosterone with much higher sensitivity to androgen receptor. 5-alpha-reductase enzyme responsible for transformation of testosterone to DHT presents in high concentrations in bald scalps.[13]

Lack of temporal regression & baldness in cases of deficiency of 5-alpha-reductase enzyme caused by mutations in its gene supports its role in androgenetic alopecia.[32,33] 5-alpha-reductase inhibitors cause cessation of hair loss progression in men, also supports its action in androgenetic alopecia.[34] Drugs inhibiting androgen synthesis, metabolism or its receptors can be used in treatment of AGA by arresting hair loss and stimulating hair regrowth.[35] Spironolactone is used to treat Female pattern hair loss (FPHL), acne and hirsutism, by competitive blocking of androgen receptors, along with inhibiting androgen production.[36] In our study 75% of male group and 80% of female group showed improvement with variable degrees after 6 months of topical 1% spironolactone treatment. In female patients, there was a significant increase in total terminal, thick terminal & total hair count while in male patients there was a significant increase in total terminal, thin terminal, vellus & total hair count after treatment with topical spironolactone. However, terminal thin and vellus hair count in females and terminal thick hair in males revealed no significant difference after spironolactone was applied. The above results suggest that topical 1% spironolactone halts

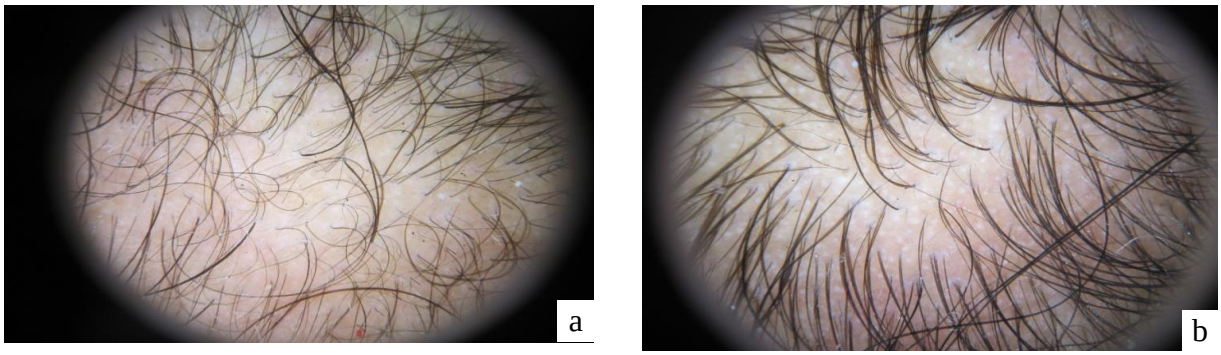

Figure 1 (a) dermoscopic picture of frontal area of a patient suffering from adrogenetic alopecia before start of treatment. (b) the same patient after 6 months of continuous topical spironolactone treatment : there is increased hair density and increased hair thickness.

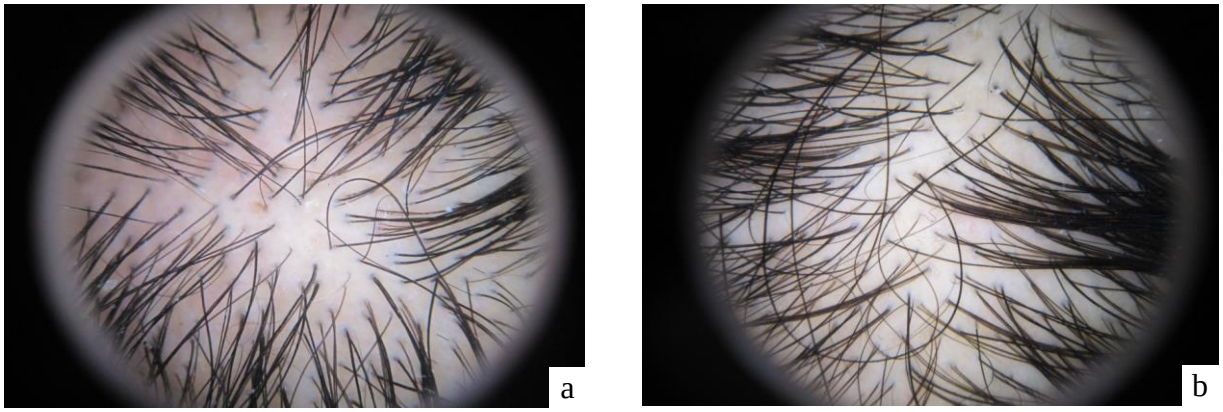

Figure 2 (a) dermoscopic picture of frontal area of another patient before start treatment. (b) the same area of the same patient after treatment; there is increased hair density.

hair loss progression with a high safety profile. This may explain why most of studies on spironolactone use in dermatology were conducted on females. However, several studies were conducted on systemic spironolactone in males complaining of androgen dependent dermatoses, for example, Sato *et al*., conducted a study on 23 male patients who received systemic spironolactone as a treatment for acne, 3 patients stopped spironolactone due to development of gynecomastia.[37]

Systemic spironolactone was used by several studies as a treatment for androgenetic alopecia. Yip and Sinclair found that systemic spironolactone is convenient in both reinstating hair growth & inhibiting progression of AGA in female patients.[35]

An open interventional study stated that systemic spironolactone has equivalent efficiency of cyproterone acetate in restoring hair growth & preventing hair loss progression.[38] Dinh and Sinclair[39] stated that patients started spironolactone 100mg/day delay early hair thinning, and higher doses of 200mg/day are required to accomplish hair regrowth.[40]

Studies supporting the efficacy of topical spironolactone in AGA are limited. In 2020, Ayman *et al*., stated that topical 5% spironolactone gives better results than topical finasteride in treatment of AGA in male and female patients with limited side effects in comparison to oral administration.[41] These results agree with our results but we used less concentration of toipcal spronolactone, also we

depended on precise detection of hair thickness and count. Our results are consistent with the results of a clinical study conducted by Dill-Muller and Zaun on 60 female patients with androgenetic alopecia, in which topical spironolactone 1% was effective in stimulating hair growth without hormonal disturbances reported, but this study did not involve male patients, and the trichogram (not dermoscope) was used to assess the results.[42] Also our results are consistent with Abdel Raouf *et al.* who used scalp biopsy (not dermoscope) to study the outcome of topical minoxidil 5% gel and topical spironolactone 1% gel in treatment of androgenetic alopecia.[43] In general, systemic administration of spironolactone is well accepted. Its main side effects are dose-dependent and are mainly allied with its antiandrogenic properties which may limit its use in males.[44]

For our knowledge, this is the first study that used dermoscopy to assess the efficacy of topical 1% spironolactone solution through precise detection of hair thickness and count in both males and females.

Conclusion

Based on the results obtained in the present study, we can conclude that topical 1% spironolactone is a safe and effective agent in females and males in management of AGA. Further studies with a large number of patients and prolonged follow-up are needed. Topical spironolactone is a good option for treatment of AGA with few adverse effects in comparison to oral administration.

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