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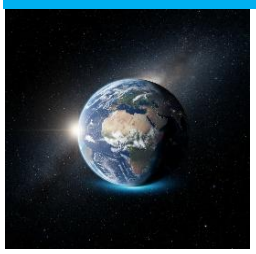

Journal of Education, Health and Sport. eISSN 2391-8306.

Journal Home Page
https://apcz.umk.pl/JEHS/index

PERZYŃSKA, Jagienka, BAGIŃSKA, Weronika, ZAŁUSKA, Urszula, KRZYŻOWSKA, Kinga, PODKOŚCIELNA, Jaśmina, RYSZKOWSKA, Kamila and PAWELEC, Natalia. The role of procedures used in the treatment of androgenetic alopecia - a literature review. Journal of Education, Health and Sport. 2026;90:70145. eISSN 2391-8306. https://doi.org/10.12775/JEHS.2026.90.70145

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 23.03.2026. Revised: 06.04.2026. Accepted: 06.04.2026. Published: 10.04.2026.

The role of procedures used in the treatment of androgenetic alopecia – a literature review

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Abstract

Introduction

Androgenetic alopecia (AGA) is the most common form of hair loss in both women and men. The prevalence of the disease increases with age. Epidemiological data show that approximately 30% of white men have AGA by age 30 years, increasing to approximately 50% by age 50 and to 80% by 70 years of age.[1] Developing effective treatments for hair loss remains a challenge for dermatology specialists due to the complex mechanisms underlying hair loss and the diverse patient demographics affected.[2] Genetic and environmental factors play a key role in causing androgenetic alopecia.

The hair loss is a result of dihydrotestosterone (DHT)'s effect on androgen-sensitive hair follicles, which leads to miniaturization of the follicle and a shortened hair growth cycle.[3]

In men, hair loss is caused by recession of the frontal hairline at the temples towards the crown of the head. It is also important to consider the correlation between increased sensitivity to DHT (dihydrotestosterone), the development of male-pattern hair loss, benign prostatic hyperplasia and a higher risk of ischemic heart disease. In women, AGA produces diffuse thinning of the crown region with maintenance of the frontal hairline (Ludwig Pattern AGA).[4] Alopecia may also occur during or shortly after menopause when the level of estrogen decreases. It may be linked with endocrine disorders, such as Cushing's syndrome, polycystic ovary syndrome or neoplastic processes in ovaries. The condition is chronic and requires long-term treatment. However, due to the persistent advance of medicine, a variety of treatment options are available, including pharmacological therapy, as well as more invasive methods.

The treatment of androgenetic alopecia mainly involves the use of minoxidil, finasteride and spironolactone. Unfortunately, pharmacological treatment is insufficient in many cases because of late-stage disease, hair follicle loss and adverse reaction to the medication. The most common side effects of topical minoxidil are hypertrichosis in the facial region and local reactions on the scalp, such as pruritus, burning sensation, erythema, papules or pustules.[5] Sexual side effects in men who have taken finasteride and dutasteride are well documented and include decreased libido, erectile dysfunction and ejaculatory dysfunction.[6] Also, increased depression, anxiety and suicidal ideation in a subset of men treated with these drugs were commonly reported in several studies.[7] Under these circumstances, the proper management is required to involve various procedures, such as: Platelet-Rich Plasma therapy (PRP), Low-Level Laser Therapy (LLLT), microneedling (MN), hair transplantation and mesotherapy.

Aim

Pharmacological therapies, including minoxidil, finasteride and spironolactone, are unsatisfactory in all patients. This study intends to evaluate the efficiency of procedures as an individual treatment of androgenetic alopecia.

Materials and methods

An extensive review of the literature was conducted using electronic databases (PubMed, Dermatology Online Journal) and textbooks. The collected information was analyzed, and the findings are presented below.

Summary

The findings of the review suggest that invasive treatment methods for androgenetic alopecia serve as a complementary approach to pharmacological therapy. Such methods include procedures like hair transplantation, platelet-rich plasma injections and microneedling which aim to stimulate hair growth, improve scalp health and increase hair density. These interventions are often used alongside ongoing pharmacological treatment to enhance and maintain long-term results.

Keywords: androgenetic alopecia, AGA treatment, hair loss, microneedling, platelet-rich plasma, hair transplantation

The state of knowledge

Platelet – Rich Plasma therapy (PRP)

Platelet-rich plasma, also known as platelet-rich growth factors or platelet concentrate, is a concentrate of platelet-rich plasma protein derived from whole blood, subsequently centrifuged to remove red blood cells.[8] Leucocytes and platelet-activating agents can be added, resulting in different types of PRP. The effectiveness of tissue regeneration stimulation depends on the concentration of platelets present in the plasma.[8] There is also a full complement of clotting factors, enriched by a range of GFs, chemokines, cytokines, and other plasma proteins.[9] The growth factors promote hair regrowth by stimulating stem cell differentiation of hair follicles, inducing and prolonging the proliferative anagen phase of hair follicles, as well as activating anti-apoptotic pathways and promoting angiogenesis to increase perifollicular vascularization

and the survival of dermal papilla fibroblasts.[11] PRP might increase vascularization, prevent apoptosis, and prolong the duration of the anagen phase.[9] A potential target of PRP could be upregulation of GFs, such as IGF-1, FGF-7, hepatocyte growth factor, and vascular endothelial growth factor. These are responsible for maintaining the hair follicle in the anagen phase of the hair cycle. The aim would be to lengthen the anagen phase by using PRP.[9]

Injections of PRP may be also combined with progesterone, dalteparin microparticles or CD34+ cells. Dihydrotestosterone (DHT) is a substance that damages hair follicles and is culpable in genetic hair loss. Progesterone inhibits 5-alpha reductase and, as a result, DHT, which allows hair growth to recover. PRP administered with progesterone naturally inhibits 5-alpha reductase, the enzyme that converts testosterone to dihydrotestosterone (DHT). Using CD34+ cells with PRP showed significant improvement in hair thickness and overall presentation.[11]

Low-level laser therapy (LLLT)

Low-level laser therapy (LLLT) is a method that uses low-intensity light, which stimulates cellular activity in tissues.[12] It is thought to exert a biomodulation/biostimulation effect on tissue, promoting anti-inflammatory effects. The exact mechanism of action in stimulating hair regrowth is not known yet, but improved cellular activity, reduced inflammation and improved microcirculation are thought to be involved.[13]

It is assumed that LLLT stimulates anagen phase re-entry in telogen hair follicles (HFs), prolongs the duration of anagen phase, and increases rates of proliferation in active anagen HFs, as well as help to promote reparative regeneration, which occurs during wound healing, and physiological regeneration, which occurs during the hair cycle, relying heavily on cell proliferation.[12] Hair density and diameter are increased, while decrease of hair shedding is observed – clinical improvement occurs. The hypothesized mechanisms of action of LLLT are: increased adenosine triphosphate (ATP) production, modulation of ROS, induction of transcription factors such as nuclear factor kappa B and hypoxia-inducible factor-1.[10] The "optical window" for biological tissue is approximately 650–1200 nm, because the tissue penetration is maximum at these wavelengths. Hence, red or near-infrared light (600–950 nm) is utilized in LLLT. [12] The most used devices have wavelengths in the range of 650–1200 nm and fluences of 1–10 J/cm^2, with a power density of 3–90 mW/cm^2. The treatment usually lasts 15–20 min, repeated three times a week for 6 months.[12] LLLT is thought to be a new safe devise-based modality for stimulating hair growth in both men and women suffering from AGA. Studies have demonstrated statistically significant hair regrowth by terminal hair count in males and females.[13]

Microneedling (MN)

Microneedling is defined as micro-puncturing the stratum corneum of the epidermis using a roller device apparatus of small fine needles. In AGA, it is often used in combination with hair growth stimulants: minoxidil, plasma-rich protein or topical steroids, as microneedling can facilitate the percutaneous delivery of topical therapies. Studies suggest that the synergistic effect of microneedling and active substances can lead to more effective therapeutic outcomes, improving both hair density and length, as well as the health of hair follicles.[10] It is also thought to stimulate hair growth via upregulation of Wnt/ß-catenin signaling and induction of vascular endothelial growth factor.[13]

MN creates micro-injuries in the skin, which stimulates angiogenesis, collagen production, and the initiation of a new anagen phase. As a result, hair follicle stem cells are activated, and the release of platelet-derived growth factor and vascular endothelial growth factor is stimulated. MN also reduces perifollicular fibrosis – a condition which frequently develops in the late stages of AGA and can compromise the effectiveness of topical and systemic therapies. Additionally, MN improves transdermal drug delivery as an adjuvant therapy, which increases the rate of absorption and accelerates the onset of action for topical medications such as minoxidil.[14] Microneedling is a generally tolerable and valuable augmentation tool for standard of care therapies and exhibits minimal side effects and low risk for serious adverse events.[15]

Hair transplantation

There are 2 primary methods of hair transplantation: follicular unit transplantation and follicular unit extraction. The latter is often preferred for younger patients and people with shorter hairstyles, as it avoids a linear donor scar. During follicular unit transplantation, harvesting of follicular units involves harvesting strips, followed by dissection into small follicular units, while follicular unit extraction involves the direct harvesting of individual follicular units.[16]

Follicular unit extraction is presently the more commonly used technique due to the following advantages: increased number of harvestable grafts, less apparent scarring, minimal graft preparation required, feasible even on tight scalps, minimal risk of nerve injury or excessive bleeding, less postoperative pain, decreased postoperative healing time, allows targeting of follicular groups based on specific size, hair diameter, or pigmentation, the surgeon can

selectively pick grafts and target hairs outside the typical donor site, such as the parietal scalp, chest, back, beard, and pubis, if needed.[16]

Nonetheless, follicular unit transplantation can be preferred in some patients due to its reported benefits, shorter operative time, less transection of follicles and a higher survival rate of the grafts, more useful for patients with advanced alopecia due to the large number of grafts from a single strip, more precise grafts enable denser packing potential, resulting in cosmetically better outcomes.[16] Overall, the most appropriate technique for a hair transplant depends on individual factors, such as the extent of hair loss, the availability of the donor area, and the desired results.[16]

The most dramatic, lasting results are often achieved by patients correcting frontal baldness. "Ideal candidates" are those that typically present with a clear, stable pattern of hair loss, characterized by at least 50% thinning or balding in 1 or more areas.[16] The scalp must be healthy, with donor hair of good quality and quantity. Furthermore, patients must have realistic expectations of the results they can achieve and have no medical conditions which could compromise surgical outcomes. The safe donor zone is in the mid-occipital region between the upper and lower occipital protuberances, typically containing 65 to 85 follicular units/cm^2.[16]

Mesotherapy as a supportive procedure

Mesotherapy with dutasteride is a novel treatment for hair loss which involves microinjection of the drug into the dermis with negligible systemic absorption.[17] Dutasteride works by blocking type I and type II 5-alpha reductase enzymes, which convert testosterone into dihydrotestosterone. In comparison to other substances used in the treatment of androgenetic alopecia, such as finasteride, dutasteride demonstrates higher efficacy because it inhibits both types of the 5-alpha reductase enzyme. The procedure is typically performed using 28-30 gauge needles or with a mesogun in sessions lasting between 10-30 minutes. To reduce musculoskeletal strain caused by performing multiple injections in one sitting, the mesogun can be utilized in some instances to deliver consistent and faster injections. There are five techniques that are commonly used and they vary in needle depth and angle of injection: the intra-epidermal technique, papule-forming technique, the nappage technique, point-by-point technique and mesoperfusion technique.[18] Regular use of dutasteride mesotherapy can lead to noticeable effects, such as increased hair density and inhibition of the hair loss process. However, the results do not appear immediately and are usually visible after several months of therapy. A series of treatments at intervals of two to four weeks is recommended, as it helps to maintain a stable level of dutasteride in the scalp.

By inhibiting the 5-alpha-reductase enzyme directly in the scalp, it helps to reduce side effects and increase the effectiveness of therapy. The procedure is particularly worth considering for patients who are in the early stages of androgenetic alopecia or who need an alternative to oral treatments.

Combination therapy

Combination therapy is the most effective method for treating androgenetic alopecia. It is based on the simultaneous use of medications that inhibit DHT or stimulate hair growth, along with in-clinic procedures. The most favorable results are achieved by combining pharmacotherapy with injectable treatments. The different modalities that can be part of systematic combinational approaches include: minoxidil, finasteride, hair transplantation, Platelet-Rich Plasma, and Low-Level Laser therapy. The process of treatment can be divided into phases: initiation phase, consolidation phase and maintenance phase. In phase one it is recommended to use topical minoxidil 5% local application once daily, with or without a peptide serum once daily with supplements of vitamins, micronutrients and protein-rich diet as necessary in the patient.[19] During the consolidation phase, a modality that affects the basic pathogenesis, oral 1mg finasteride and PRP (once a month for 3-4 months) is initiated.[19] At the final phase of treatment topical minoxidil with oral finasteride are used daily. Also, PRP is recommended in the month of drug holiday to compensate for lack of finasteride effects. Hair transplantation may be needed in selected cases as per requirements of the patient.[19]

Discussion

Like most meta-analysis studies, this one is not free of limitations. Many studies, from different research centers and years, were combined to reach the conclusions present in this paper. All the methods discussed have their advantages, disadvantages and are on different levels of development and understanding.

RP is easily harvested from patients' own blood, making PRP therapy a safe, in-office procedure.[11] Its mechanism of action particularly needs to be studied further. There is intensive ongoing debate regarding the ideal volume of PRP to administer, the frequency of application, the exact site of administration of PRP, and which technique/preparation system of manufacture to choose.[9]

Also, a system of characterization should be selected for better standardization and easier sorting and interpreting of the data. More randomized controlled trials should be conducted to provide scientific evidence and avoid bias.[9] Moreover, some studies report significant increases

in hair density of patients, even if only the placebo treatment was used. Microstimulation by needle puncture itself might exert beneficial effects on hair growth – a technique used in microneedling, so it is hard to distinguish which method produces these results.[11]

Furthermore, combining PRP injections with other hair restoration treatments, such as finasteride (male patients), minoxidil, low-level light therapy, and spironolactone (female patients), may enhance the overall efficacy. PRP injections may also improve the outcome of hair transplantation and may soon be part of the pre-treatment and post-treatment maintenance protocols. After treatment, patients can resume normal daily activities, including returning to work the following day.[8] The risk of adverse effects is small, but includes scalp sensitivity and mild scalp scaling, and there is a risk of infection as well. Also, patients with a history of malignancy, platelet disorders, anemia, bleeding disorders, pregnant women, or immunocompromised patients cannot become candidates for PRP.[15]

LLLT is a potentially effective treatment option for patients suffering from non-scarring alopecias, who do not respond or are not tolerant to standard treatment of hair loss. It is also efficient when used as concomitant therapy to finasteride and minoxidil. Additionally, it can be used during immediate period of post-hair transplant surgery to facilitate the healing process and enhance viability and earlier growth of the grafts. The exact mechanism of action in stimulating hair regrowth is not yet known – further understanding of this method will lead to a better and more focused treatment. Studies have shown that LLLT resulted in a significant increase in hair density. Moreover, low-frequency treatment might produce better results than high.[13] Studies suggest that patients with male AGA (Hamilton–Norwood III and IV) and female AGA (Ludwig I and II) respond best and LLLT accelerates the process of hair regrowth. The incidence of adverse effects in LLLT is low and includes the temporary onset of telogen effluvium developing in the first 1–2 months after commencing LaserComb treatment, but disappearing on continued application. Also, if dysplastic or malignant lesions on the scalp are present, they could be stimulated to grow by proliferative effects of LLLT.[12] Other studies report temporary hair shedding, pruritis, tenderness, and acne.[15]

Patients looking for quick improvement as well as those suffering from hair loss refractory to standard of care treatments may benefit from microneedling. It may serve as a generally tolerable and valuable augmentation tool in hair loss therapy.

Microneedling alone can stimulate neovascularisation, growth factor activity and Wnt protein expression. However, hair growth stimulants: minoxidil, plasma-rich protein or topical steroids administered through microneedling can facilitate the percutaneous delivery of topical therapies, improving the results of the treatment.[13] There is no agreement as to which needle depth,

treatment duration, and device type produce best results[14], which means that there is no standardization of them yet.

The wide variety in microneedling therapy parameters can make establishing a standard protocol for the treatment of AGA difficult.[15] It is, however, vital that such protocol be established, so that right parameters can be applied for the best outcome. Overall, microneedling exhibits minimal side effects and the risk for serious adverse events is low. The potential adverse effects are pain during treatment, transient pinpoint bleeding, erythema, and even enlargement of lateral cervical lymph nodes, pruritis, seborrheic dermatitis, headache and infection, as the microtrauma is created. Nonetheless, there are some studies that reported no adverse events.[15]

Hair transplantation is also an effective method of treating androgenetic alopecia, particularly in more advanced stages of the disease. However, this method is the best for individuals aged 30-60, when the progression of hair loss is more predictable and the process of hair shedding no longer advances as rapidly. This treatment method may not be effective for young individuals, particularly those under the age of 25, because hair loss may continue to progress and the results of the procedure may become irregular. The advantages of FUE are that no scar is usually present in donor area, which means that patients can keep hair short after surgery. It is ideal for patients who have less scalp laxity, those who have undergone the strip method in the past, those who are prone to hypertrophic scarring, where hair from other parts of the body has to be used and where postoperative care needs to be minimal. On the other hand, FUT is labor intensive, time consuming, needs more assistants, and requires microscopic dissection of hairs, which can only be performed by skilled personnel.[20]

Mesotherapy is an ideal complementary treatment to pharmacological therapy. Regularly performed mesotherapy can help reduce excessive hair loss and improve hair density. This method is especially recommended for patients who primarily want to improve the condition of the scalp, rather than achieve immediate significant hair density. It is likely to be less effective in individuals with psoriasis or seborrheic dermatitis because injecting active substances into areas affected by inflammation can exacerbate irritation and limit the ability of hair follicles to regenerate properly. The injections increase the risk of complications.

Patients with disrupted skin microflora and natural skin barrier may not absorb the substances administered during mesotherapy evenly, and therefore a different, more effective treatment method should be chosen for them.

Combined therapy is especially recommended for patients in the early to moderate stages of androgenetic alopecia, when a single treatment method is insufficient. It is also an appropriate treatment for individuals who want to achieve better and more lasting results by combing hair growth stimulation with the inhibition of hair loss. Patients need to participate regularly in a series of procedures to satisfactory results, so this method is not suitable for those with limited time. Individuals suffering from chronic inflammatory skin conditions, psoriasis, or seborrheic dermatitis should not undergo combined therapy, as it carries the risk of exacerbating the underlying disease. Injectable procedures can mechanically irritate the skin and trigger a flare-up of psoriasis.

Conclusion

Treatment of androgenetic alopecia requires an individual approach, as the effectiveness of each method depends on numerous factors, including the stage of hair loss, the patient's age, the condition of the scalp, and the presence of coexisting dermatological conditions. Due to the direct administration of active substances into the scalp, it is possible to achieve a more effective impact on hair follicles and improve the conditions for their functioning.

Each method has its advantages and limitations, some are most effective in the early stages of the condition, while others, are used for more advanced hair loss. Many treatments require regularity and patience, and their effectiveness may be limited in cases of inactive hair follicles or active skin diseases. Combined therapy gains an increasing importance, as it allows for simultaneous stimulation of hair growth and inhibition of hair loss, enhancing the chances of achieving satisfactory and long-lasting results. Nevertheless, even combining methods does not guarantee full hair regeneration and requires careful approach to the individual needs of the patient.

In summary, an effective treatment of androgenetic alopecia requires a comprehensive assessment of the patient, a conscious selection of a single method or a combination of therapies, and consideration of the potential limitations each method.

A personalized strategy not only improves treatment efficacy but also minimizes the risk of complications and ensures patient safety.

Disclosure

Author's contribution

Conceptualization: Jagienka Perzyńska and Weronika Bagińska Methodology: Jaśmina Podkościelna Software: Kinga Krzyżowska Validation: Kamila Ryszkowska and Urszula

Załuska Formal analysis: Natalia Pawelec and Weronika Bagińska Investigation: Natalia Pawelec and Urszula Załuska Resources: Kinga Krzyżowska Data curation: Jaśmina Podkościelna Writing-original draft preparation: Jagienka Perzyńska and Weronika Bagińska Writing-review and editing: Urszula Załuska and Kinga Krzyżowska Visualization: Kamila Ryszkowska Supervision: Natalia Pawelec Project administration: Jagienka Perzyńska and Jaśmina Podkościelna Fuding acquisition: no specific funding.

All authors have read and agreed to the published version of the manuscript.

Funding statement

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data availability Statement

Not applicable.

Conflict of Interest Statement

The authors deny any conflict of interest.

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