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The diagnosis and treatment of androgenetic alopecia: a review of the most current management

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ABSTRACT

Androgenetic alopecia is a widespread problem in contemporary dermatology, as it may also affect many young patients, in particular males, making them more prone to anxiety and depression which may be caused by a distorted body image. These behavioural problems may occur in older individuals as well. That is why, there is an obvious need for further development in that area of dermatology, which should also include discovering new therapies. In men, the diagnosis of androgenetic alopecia is quite simple, and the treatment usually involves incorporating minoxidil and/or finasteride. Switching from topical minoxidil to its systemic form as well as from finasteride to dutasteride may give better results in some patients. In general, male pattern hair loss (MPHL) is a chronic disease that may demand pharmacological treatment in the long term, which is often unlimited. Therefore, and also considering the patients' concerns involving the systemic usage of 5α-reductase inhibitors as well as the limitations of current therapies, some specialists use topical finasteride, dutasteride in mesotherapy and many other additional modalities. When it comes to female pattern hair loss (FPHL), in most cases it is also a chronic entity, which especially in younger women demands performing extended lab testing in the search for potential hyperandrogenism. It is necessary to remember that especially in women the condition may be triggered by many environmental and other additional factors, so taking that into consideration may be helpful in some patients.

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Keywords: androgenetic alopecia, hair loss, minoxidil, finasteride

INTRODUCTION

Different types of alopecia can be associated with decreased hair growth, increased hair loss, conversion of thick terminal hair into thin follicular hair, congenital or acquired abnormalities of the hair shaft as well as inflammatory skin diseases. Androgenetic alopecia (AGA) is the most common type of alopecia. This condition can be further divided into two categories: male androgenetic alopecia/male pattern hair loss (MAA/MPHL) and female androgenetic alopecia/female pattern hair loss (FAA/FPHL). It is established that AGA affects at least 8 in 10 men below the eighth decade of life including up to half of the middle-aged men, while FPHL is less common, affecting almost half of the women below the age of 70 including approximately 30% of middle-aged women. Androgenetic alopecia is far more common in the Caucasian population and its incidence becomes higher with ageing [1, 2].

Androgenetic alopecia most commonly manifests by an excess of hair loss. Gradually progressing miniaturization of hair follicles results in the heterogeneity of hair shafts. Typical changes within the hair cycle including anagen shortening as well as telogen extension lead to the conversion of terminal hair into their less developed precursors. Clinically manifested shortening of hair can be observed, which can eventually lead to the complete loss of hair shafts within the hair follicles. Androgenetic alopecia is classified as non-scarring alopecia. However, with the chronic nature of the condition, follicular atrophy can occur with its clinical, trichoscopic and histological features at a very late stage of the disease [3].

The pathogenesis of AGA is multifactorial with well-recognized aetiopathological factors including genetic predisposition, impaired and excessive response of hair follicles to androgens within the scalp and inflammation

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in hair follicles. Genetic factors are thought to be responsible for approximately 80% of the general predisposition to balding in the mechanism of MPHL, in which at least 250 genetic loci are yet discovered and associated with the process. However, in FPHL the role of genetics is way less obvious with the highest probability of genetics engagement in women with an early onset of AGA [4]. Male pattern hair loss is a strictly androgen-dependent disease, while in women the role of androgens in mediating hair loss remains uncertain and needs to be further investigated [5]. In addition, many new genes and signalling pathways, i.e. hypoxia-inducible factor (HIF-1) signalling pathway (*EGLN1* and *EGLN3* genes) and Wnt pathway inhibitors (*PEDF*, *SERPINF1*, *SFRP2* genes), have been recently identified in a male model of AGA as potential therapeutic targets for the disease [6].

Scalp testosterone is converted into 5α-dihydrotestosterone (DHT) by an enzyme 5α-reductase type II. DHT acts directly on the androgen receptors (AR) of hair follicles leading to their miniaturization in androgen-dependent areas within the scalp of affected individuals in the mechanism of anagen shortening. In women, this phenomenon is far less common, because oestrogens can prolong the anagen phase of the hair cycle. That is why AGA is way more common in women after menopause. The other very important factor is that women have higher activity of the aromatase which converts androgens into oestrogens in the peripheral tissues and the scalp [5, 7, 8].

In both sexes, androgen-dependent areas of the scalp are defined as those with a high concentration of androgen receptors (AR). Parietal and frontal regions in both sexes as well as frontotemporal angles in men are generally included in this category as areas affected by the disease. The reason for that particular difference in engaged site distribution between the two sexes is that men have about three times higher expression of AR within the frontal area in comparison to women. Moreover, most men with AGA have normal levels of serum androgens, while 1 in 3 women have AGA accompanied by hyperandrogenism. Increased serum levels of androgens in women may be caused by many endocrinological entities including the most common one which is polycystic ovary syndrome (PCOS). The proper diagnosis and management of the diseases potentially causing hyperandrogenism in women, which should be done in cooperation with endocrinologists and/or other specialists, is essential for therapeutic success [5, 9].

The last component which takes part in the etiopathology of AGA is the role of micro-inflammation in hair follicles. The inflammation may be caused and triggered by exogenous factors such as air and/or other environmental pollution. The other factors involve the general state of the human body as they are called the endogenous factors. Probably the most well-known factor belonging to that category is the metabolic syndrome that upregulates the expression of pro-inflammatory cytokines. This is the reason why obesity, hyperlipidaemia and hyperinsulinemia may contribute to the development of AGA. The other thing is that incorrect nutrition as well as vitamins and microelements deficiencies may trigger and accelerate the whole process of effluvium. This is also true when it comes to coexisting diseases such as thyroid disorders [9–11].

DIFFERENCES IN CLINICAL PRESENTATION OF ANDROGENETIC ALOPECIA IN MEN AND WOMEN

Macroscopic patterns of AGA differ depending on the patient's gender which exactly corresponds to distinct pathoaetiology of the same entity in men and women.

Initial MPHL typically shows a decrease in hair density and thickness on the temples which are frontotemporal angles. This is due to the frontal hairline recession marked as an M-shaped anterior (frontal) hairline which keeps receding posteriorly as time goes by. The other side of the AGA involvement in men is the vertex. The disease in men can be assessed by the usage of the Norwood–Hamilton scale which is a commonly used measure for evaluating the advancement of MPHL. It consists of types (stages) from I up to VII and the higher the number, the more advanced the process of hair loss is. The initial shedding of the vertex area accounts for the IIIv (III vertex) stage of the disease advancement.

Female pattern hair loss may present as hair loss in frontal and parietal regions which corresponds to the Ludwig type of AGA in women that is usually assessed by the Ludwig scale. The other type of hair loss in women with AGA is the Olsen type of FPHL. It is characterized by progressive loss of hair only in the mid-frontal scalp and this is most commonly called a "Christmas-tree pattern hair loss". In most cases, in women with androgenetic alopecia, the frontal hairline stays preserved which is a characteristic that morphologically differs FPHL from the same entity in men. In women with progressing frontal hairline recession, the condition needs to be differentiated from frontal fibrosing alopecia [10, 11].

DIAGNOSIS OF ANDROGENETIC ALOPECIA

In men, diagnosis of androgenetic alopecia is based on the clinical assessment of a patient as well as an optional trichoscopy. Trichoscopic evaluation is not mandatory in men to conclude a diagnosis, but nowadays it is advised to perform it in order to further assess the efficacy of applied treatments. What is more, performing trichoscopy in newly appointed patients seems to be crucial when it comes to looking for potential coexisting diseases of the scalp. Using these two modalities (clinical and trichoscopic examinations) allows one to make a clear diagnosis. However, in women, there is a greater need for additional

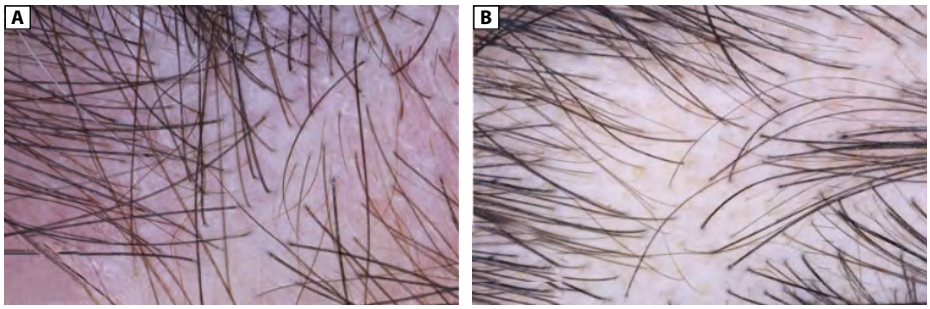

Figure 1A, B. The hair shaft thickness heterogeneity (derived from hair follicles miniaturization); an increased proportion of follicular units with an only hair shaft

examinations, which in most cases should include hormonal tests evaluating androgens serum levels (androgen profile), other blood tests (including vitamin D serum level, blood morphology, iron blood level as well as serum levels of vitamin B12, TSH and prolactin), optional biopsy in case of more concerning and unsure clinical manifestations as well as other specialists' consultations. In many cases of FPHL, a quite long diagnostic pathway may be necessary to make the final diagnosis and exclude other potential diseases. Trichoscopy can be performed using a handheld dermoscope or a videodermatoscope. In general, videodermatoscopy gives more detailed images, which can account for an easier diagnosis. The other very important factor is that videodermatoscopy allows making photographic documentation of a particular patient's trichograms. It further enables a doctor to compare the initial trichoscopic evaluation with the local state during the treatment. It can reduce the use of unworking and ineffective treatment modalities in non-responding patients, as in most implemented therapies the initial reassessment should take place approximately six months after the introduction of a proposed treatment. However, in order for many treatment modalities to develop maximum therapeutic effects, more time is usually needed and that most often accounts for 1 to 2 years. The time needed for a particular response may also be very distinct in different patients, taking into consideration their general health and other factors such as received basal treatment. Therefore, it is reasonable to look into each case separately and with much caution [4, 11].

TRICHOSCOPIC SIGNS OF ANDROGENETIC ALOPECIA

Figures 1A and B present the hair shaft thickness heterogeneity (derived from hair follicles miniaturization); an increased proportion of follicular units with only the hair shaft. Figure 2 depicts perifollicular hyperpigmentation. Figure 3 shows yellow dots (account for empty follicular openings); the increased proportion of vellus hair.

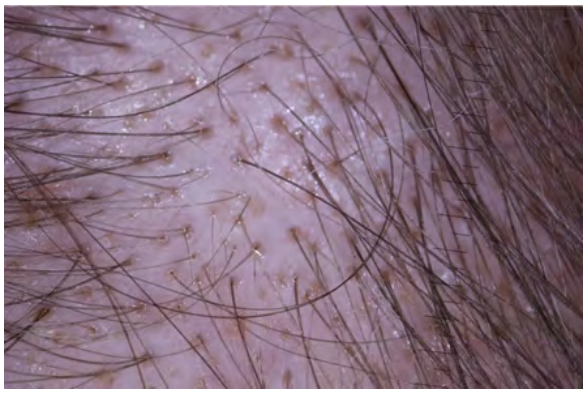

Figure 2. Perifollicular hyperpigmentation

Figure 3. Yellow dots (account for empty follicular openings); the increased proportion of vellus hair

TREATMENT OF ANDROGENETIC ALOPECIA

Topical minoxidil is registered for the treatment of androgenetic alopecia in both women and men, while oral finasteride in a daily dose of 1 mg is exclusively registered in the management of male androgenetic alopecia. Exist treatment modalities that are derived from these well-known and broadly used remedies. Completely new approaches are also being studied. In this category are included pharmacological and nonpharmacological methods which are

becoming successfully used in daily clinical practice. They are also a vital subject of the research as they may gradually become the basis for the potential changes in official recommendations of the scientific societies including the Polish Dermatologic Society as well as international societies. An example of such actions may be the introduction of oral finasteride for the treatment of androgenetic alopecia in women and the use of minoxidil in its systemic form in both sexes [12].

Before starting any treatment schemes, it is important to inform the patients that a positive lifestyle change including loss of weight in case of an impaired body mass index (BMI), introducing a well-balanced diet, exercising more often and with more intensity, well-performed treatment of comorbidities and supplementation of vitamins and microelements in case of their deficiencies can be helpful in the management of most cases, as it can enhance a patient's chance of a good response to the proposed treatment. Especially important seems to be an active control of the vitamin D serum level and a thorough treatment of thyroid and hormonal impairments [11].

Minoxidil

Minoxidil is transformed into an active metabolite (minoxidil sulphate) by an enzyme sulfotransferase family 1A member 1 (SULT1A1) that is expressed in the outer root sheath cells of hair follicles. The enzymatic activity of SULT1A1 varies between individuals and the higher it is, the better clinical response to minoxidil should be expected [13]. This characteristic could be utilized in tests assessing the enzymatic activity of SULT1A1, which would then allow for the prediction of treatment outcomes in individual patients and consequent direct personalization of the therapeutic process. However, such tests are not yet available in clinical practice. On the other hand, the fact that minoxidil sulfotransferase is an enzyme and that in the cells there are no endogenous compounds that act as its enzymatic adjuvants, have prompted researchers to look for exogenous compounds that could enhance the enzyme activity. This is especially important since only 3 to 4 in 10 patients respond to topical minoxidil. In most patients, therapy with topical minoxidil does not bring any change, i.e. density and thickness of hair stay the same, as these patients are called non-responders. A small cohort study from 2022 showed the effectiveness of using a minoxidil adjuvant therapy [14]. Nowadays, booster-like substances are a subject of research, as most information about them is yet to be discovered. However, in a small study conducted by Sharma et al. [15], topical tretinoin has been shown to convert 43% of primarily non-responding patients into responders, as tretinoin is thought to upregulate the activity of SULT1A1. Therefore, it may be that the topical formula consisting of minoxidil and tretinione can bring a positive change in non-responders with a particularly low activity of SULT1A1.

Minoxidil exhibits a multidirectional activity. Its main mechanism of action is based on inducing the vasodilation of hair follicles' microvasculature, which improves their oxygenation by providing blood rich in oxygen and nutrients. The biochemical process of converting testosterone to DHT is more effective in low-oxygen environments and the oxygen increases the conversion of androgens to oestrogens by the aromatase. Therefore, increasing oxygen concentration in the scalp allows for reducing DHT levels which may further inhibit the process of hair follicles miniaturization. The clinical efficacy of minoxidil in hair restoration medicine also comes from its anti-inflammatory action and VEGF--dependent β-catenin pathway inducement. Minoxidil may also exhibit anti-androgenic properties by lowering the expression of the type II 5α-reductase gene. The multifaceted activity of minoxidil leads to anagen extension, which results in increased hair density and thickness. This effect is particularly noticeable in the vertex and the mid-scalp areas, while it is seen to a lesser extent in the frontal region. Strongly androgen-dependent areas such as the temples and the frontotemporal angles are especially demanding to achieve good results with the management based on monotherapy with minoxidil [16, 17].

Minoxidil in its topical form is traditionally used to treat patients with androgenetic alopecia as a solution or a foam at 2% as well as 5% concentrations. Men typically achieve the best results with 5% preparations, while women achieve similar results with both 2% and 5% preparations. Before starting the treatment regimen with topical minoxidil, a patient needs to be informed that it is important to carefully take care of scalp hygiene and to preferably use trichological scalp scrubs in order to cleanse thoroughly the outlets of hair follicles, as it may improve the penetration of minoxidil through the scalp and therefore enhancing its therapeutic effect. Most recently, the use of minoxidil in systemic treatment is becoming increasingly popular. The main advantage of this route of administration is that it is easier for patients to adhere to the therapeutic regimen. This is particularly important for patients who have difficulties following topical treatment. In addition, systemic use does not lead to any unwanted side effects associated with topical therapy, such as an unfavourable cosmetic effect, changes in texture and/or colour of hair, excessive dryness and itching of the scalp, including the risk of developing potential contact dermatitis in the targeted area. Introducing the therapy with systemic minoxidil seems to be the method of choice in patients that do not respond adequately to topical minoxidil, because oral minoxidil is thought to produce better results in patients with an insufficient SULT1A1 activity. Administered systemically minoxidil is metabolized in the liver, which has its own

fraction of the enzyme and therefore very probable is that it allows for increasing the bioavailability of minoxidil [18]. The combination of oral minoxidil with topical minoxidil may also be beneficial in some patients. The adverse effects of therapy with oral minoxidil are usually mild, especially in younger patients and include the following: hypertrichosis in various areas of the body and the risk of inducing orthostatic hypotension as well as oedemas in different parts of the body, most commonly in lower extremities. Hypertrichosis is the most reported adverse effect in women, while the others are relatively rare. The risk of triggering potential side effects becomes higher with increasing the daily dosage of minoxidil. Special caution during the initial phase of treatment may be recommended for patients with cardiovascular diseases or with an increased risk of unfolding cardiovascular events. It should be noted that the transient telogen effluvium may be the adverse effect of treatment with minoxidil. It typically appears from the sixth to the eighth week of the use and usually resolves gradually with the continuation of therapy. Another episode of the telogen effluvium may also occur approximately 3 months after the discontinuation of treatment. The initial dose of oral minoxidil in men usually accounts for 2.5 mg per day and the therapeutic dose, ranging from 2.5 mg to 5.0 mg per day, is determined individually. However, in many cases, a dose of 1.25 mg per day may be the one to start with. Women typically receive lower doses, ranging from 0.25 mg to 1.25 mg per day with the initial dose of 0.25 mg per day [19–22]. In women, the effects of the use of 0.25 mg of minoxidil can often be enhanced by adding 25 mg of spironolactone per day [23]. The clinical and trichological reassessment should take place 6 months after the initiation of therapy in order to mainly determine if it is needed to increase the dosage.

Finasteride

Finasteride, as a selective and specific inhibitor of the type II 5α-reductase, is a medication with a direct anti-androgenic effect and therefore its mechanism of action corresponds with the main pathomechanism of the MPHL. Finasteride inhibits further hair loss and causes partial hair regrowth in over 95% and 66% of men, respectively. In younger patients, especially those under the age of 40, a better therapeutic effect can be expected, which is also highly individualized and may depend on the usage of concurrent therapies [24]. The first trichoscopic examination to evaluate the treatment effectiveness should be performed six months after the initiation of therapy and the other one after another six months in order to examine the overall finasteride efficacy in a particular patient. However, some patients may even need up to 2 years in order to exhibit the maximal therapeutic effect. The recommended daily dose of finasteride for men with AGA is 1 mg. It was established based on clinical trials that assessed the effectiveness of doses ranging from 0.2 to 5 mg per day. The 1 mg dose represents a balance between going for high treatment efficacy and limiting the possibility of developing adverse effects. Finasteride is a highly effective drug in the treatment of MPHL. However, there is a high level of fear among men with AGA regarding the drug. Adverse effects in the form of common sexual dysfunctions and neuropsychiatric disorders such as depression, occur rarely and force the discontinuation of therapy in about 1% of men during the initial first year of the treatment. Similar adverse symptoms may be the components of the so-called "post-finasteride syndrome", in which the symptoms persist for some time after discontinuing the therapy. However, special caution should be followed in men with a history of depressive disorders. In this group of patients, the nocebo effect may be more common than in other men [25–28]. The efficacy of finasteride in the treatment of MPHL is greater in comparison to 5% minoxidil and combining finasteride with 5% minoxidil allows for achieving even better treatment results [29, 30].

Despite the fact that based on various trials, the adverse effects during the therapy with finasteride occur in 0.8–6% of men, which accounts for being only slightly higher than in the placebo groups, some men because of these side effects cannot or simply do not want to continue the treatment considering the need for a long-term therapy, which has been an impulse for the research teams to try to develop new treatment regimens [11]. The goal has always been to find a way to provide finasteride directly to the scalp by bypassing the systemic circulation, which would cause much fewer potential adverse effects associated with the systemic use as well as being at least as effective in reducing the level of DHT within the scalp.

Currently, the most well-known method which is based on that postulate is topical finasteride. Results of various clinical studies indicate that this may be an equally effective method as the systemic treatment, which most importantly would minimize the risk of developing potential side effects. Conducted by Caserini et al. [26] randomized controlled trial, has proven that the treatment with 0.25% topical solution of finasteride is as much effective in promoting hair growth as the 1 mg tablets with both modalities causing alike decrease of serum DHT level. However, oral finasteride was found to provide a significantly higher plasma concentration of the medication than its topical equivalent [26]. In a newer randomized controlled trial from 2021, it was established differently, that the decrease of DHT serum level is significantly higher in the systemic use of finasteride than in its topical formula (respectively 34.5% *vs.* 55.6%) [27]. Even though the usage of topical finasteride is not officially recognized by the FDA or any other scientific societies, in

particular, countries such as Spain, ready-made preparations of topical finasteride are accessible for patients. However, they are not available on the Polish market and therefore may only be used as components of other topical remedies. However, the use of them is not recommended, because the pharmacodynamics of such preparations, which can be mainly prepared in pharmacies, cannot be yet specified and the other thing is that the bioavailability of them cannot be maintained constant or even assessed. Finally, larger randomized trials are needed to determine the following factors concerning a preparation: the most effective finasteride concentration, the most optimal scheme of its production and usage as well as exploring new potential pathways of providing finasteride directly to the scalp. The other thing that needs to be cleared is how often the spectrum of adverse effects associated with topical use really happens in comparison to the systemic treatment [31–33].

Another alternative to oral finasteride may be oral minoxidil at a high dose of 5 mg per day. According to the Gupta group analysis, the use of 5 mg of minoxidil in monotherapy may be more effective than 1 mg of finasteride in monotherapy. However, 5 mg of finasteride may probably give better results than monotherapy with 5 mg of minoxidil as well as with 1 mg of finasteride. However, the introduction of finasteride at such a high dose may relate to a way higher risk of developing sexual and neuropsychiatric side effects [34].

Dutasteride

Dutasteride is a selective and specific inhibitor of both I and II 5α-reductase isoenzymes, as it inhibits the I isoenzyme 100 times greater than finasteride and respectively the isoenzyme II 3 more times than finasteride, which accounts for decreasing the serum DHT level by 90% and makes dutasteride more potent than finasteride in decreasing serum and scalp levels of DHT. Dutasteride is an off-label medication used in the management of AGA in men who have not achieved desired therapeutic effects during 12 months of 1 mg finasteride treatment or for those who have not produced any response to finasteride at all ("finasteride resistance"). Due to its greater efficacy and superiority over finasteride in the treatment of MPHL, which has been demonstrated in randomized studies, its use as a first-line drug in men with advanced hair loss can be considered. However, many dermatologists are of the view that the treatment should always be started with 1 mg of finasteride to figure out if there are any side effects of the therapy. There are particular reasons for such precautions. Finasteride's half-life is relatively short, accounting for 4.5 h, which allows for its fast elimination if the treatment is discontinued. Therefore, starting with finasteride may be reasonable, as if after 6 months of its use, the clinical outcome is not satisfying and there are not any side effects, then the patient can potentially switch to dutasteride. The standard dose of dutasteride accounts for 0.5 mg per day. This dose of dutasteride has been proven to be more effective than 1 mg or 5 mg of finasteride as well as 5 mg of minoxidil [34]. The profile of adverse effects caused by the treatment with dutasteride and the frequency of their occurrence seems to be quite similar to those associated with finasteride [35–37].

Currently, the research is focused on the use of dutasteride in mesotherapy. This method is already offered by some clinicians, mostly as part of clinical trials. In most cases, the procedure of mesotherapy with dutasteride is repeated every three months, since dutasteride has a very long half-life accounting for 4–5 weeks [38]. A retrospective study in real clinical practice, that has been conducted on 541 patients by Saceda-Corralo et al. [39], showed that the method may be effective for both women and men, who wish to avoid oral therapies. No serious sexual or neuropsychiatric side effects have been described, with the pain being the most frequent one. Additionally, in a different trial with the supervision of the same author, with 5 men and 1 woman taking part in the study, no significant changes in DHT serum levels have been described following the treatment [40].

Finasteride and dutasteride in the treatment of FPHL

5α-reductase inhibitors: finasteride and dutasteride are also being used for the treatment of androgenetic alopecia in women as an off-label therapy. However, their introduction to the management of FPHL remains limited to only specific clinical situations such as ineffective treatment with other modalities including oral minoxidil, antiandrogens such as spironolactone, other complementary non-pharmacological methods and with the exclusion of potential endogenous factors that may be causing the hyperandrogenism. It should be remembered that both finasteride and dutasteride are teratogenic and cannot be used during pregnancy. Effective contraception is necessary for at least 1 month after the discontinuation of therapy with finasteride and respectively 6 months after the discontinuation of dutasteride. The recommended dose of finasteride for the management of FPHL is higher than the standard dose used in MPHL and that accounts for 1 to 5 mg per day with a dose of 2.5 mg per day, being the one most used. When it comes to dutasteride, a dose dedicated to women is the same as the one that is recommended for men and accounts for 0.5 mg per day [41].

Other treatment modalities used in the management of androgenetic alopecia

The other therapies are generally used as complementary methods to the basic treatment, which remains in accordance with the official guidelines that are promoted by

the scientific societies as the one having the highest class of evidence according to evidence-based medicine. However, these methods are sometimes very effective in daily clinical practice, as they only need further research to prove it. Most commonly, they are used as components of the so-called multimodal therapy, which uses various therapeutic methods that very often may allow the patient to achieve better and more satisfactory results. The use of these additional methods depends directly on the knowledge and experience of a performing doctor. Sometimes they can be used in monotherapy. This particular situation can occur in patients with contraindications to the other methods of treatment or when the patient does not give consent to the proposed therapy [42].

Mesotherapy with platelet-rich plasma

It is a mesotherapy technique using the patient's autologous plasma with a high content of platelets and associated with the platelets growth factors such as PDGF, EGF, VEGF, ECGF, TGF-β, IGF and CCL2. These molecules are widely known to promote hair growth based on the inhibition of inflammation, the promotion of bulge stem cell differentiation and the stimulation of angiogenesis. Currently, the use of PRP is probably the most effective method, among other techniques utilizing mesotherapy, in the management of AGA. Mesotherapy with platelet-rich plasma (PRP) is becoming very close to officially being included as part of the evidence-based medicine guidelines for AGA treatment in both sexes. To achieve that, the proper alignment of the knowledge needs to be done, as each practitioner may have their own method of plasma preparation. The heterogeneity of the used regimens is obvious, however in all cases, it is especially important to provide the most effective platelets count, as 1 microliter of plasma needs to contain around 1–1,5 million platelets, which corresponds to 2- to 4-times higher than in the blood. A total plasma volume of 5–7 mL is typically used during the single treatment session, with the typical dose accounting for 0.05 to 0.1 mL per cm^2 of the scalp [43, 44]. To determine the effectiveness of the method in a particular patient, it is necessary to perform 3 treatment sessions at intervals of 1 month between each one. Mesotherapy with PRP is very commonly performed in women with AGA, especially in situations when the desired results cannot be reached with minoxidil, as it seems to be especially effective in the management of FPHL. In men, the highest chance of getting the most proper response have patients with the disease advancement of II to V in the Norwood–Hamilton scale. There are still a few things that need to be further investigated. That includes getting to know what the long-term effects of the PRP therapy (that includes an adequate follow-up) can be as well as its potential long-term side effects. The other thing that needs to be further investigated is discovering potential pathways for the method improvements, especially when it comes to providing the preparations into the scalp [42, 45].

However, PRP demands anticoagulants to work properly and therefore it is not a fully autologous material. This drawback has been solved by the implementation of injectable platelet-rich fibrin (PRF). It contains exactly the same components as the PRP with a few additional ones such as type-I collagen, lymphocytes and the growth factors of lymphocytes. Injectable platelet-rich fibrin is thought to be a fully autologous material. Its efficacy in clinical practice seems to be following the one of PRP. Despite this fact, more randomized trials need to be performed in order to be able to choose the method that would be more individualized and directly respond to the particular patient's needs [46].

Low-level laser therapy

Low-level laser therapy (LLLT) is the type of therapeutic method that is known on the Polish market as so-called low-energy laser therapy. The method is based on the use of red and infrared light in the range of wavelengths between 600 nm and 950 nm with low energy of 1–4 J/cm^2. Lasers or light-emitting diodes (LEDs) are used to emit light with the desired parameters. Most commonly available on the market products are equipped with lasers. Many of these devices have been officially approved by the FDA for use in the treatment of androgenic alopecia in both men and women (FDA-approved/FDA-cleared devices). It is believed that the LLLT mechanism of action involves absorption of the light with a specific wavelength by the mitochondrial cytochrome C oxidase in the cells of various parts of the hair follicles such as outer root sheath cells, hair matrix cells and dermal papilla cells. This leads to a two-way increase in the synthesis of nitric oxide (NO) and the modulation of reactive oxygen species (ROS) synthesis. The result of these two processes is an increased proliferation of cells building the hair units, an increase in the synthesis of growth factors such as FGF2, HGF, and VEGF and finally an increase in the transmission of signals in the Wnt/β-catenin pathway within the hair matrix cells. Additionally, by reducing the synthesis of pro-inflammatory factors and increasing the synthesis of anti-inflammatory factors, there is a modulation of the immune activity around hair follicles, which may reduce the inflammatory process. All these effects can lead to the promotion of hair growth [47, 48].

Most clinical studies have shown that LLLT is a safe and effective way to treat AGA in both women and men, as it increases hair density and strength. In some patients, the LLLT technology can even produce similar results to oral finasteride or topical minoxidil [48, 49]. The exact parameters of the therapy that would allow the patients to achieve the best possible results are still the subject of research, but

most used devices produce the following light parameters: wavelength in the range of 635–650 nm, energy density accounting for 4 J/cm^2 with the power of 5 mW. However, in the randomized trial of 90 patients, it has been proven that the combined therapy with the red light of 665 nm and infrared light of 808 nm produces better results than the monotherapy with light of 665 nm [50]. A single session of treatment, depending on a particular device and the used method, usually lasts from 6 to 20 minutes and most commonly should be performed three times a week [48–51].

The use of combination therapy with the LLLT and 5% minoxidil has been proven to be more beneficial than monotherapy with 5% minoxidil. In the randomized trial conducted in 2019, a statistically significant effect of increasing the hair density and diameter was observed with the combined therapy in comparison to a monotherapy with 5% minoxidil [52]. Low-level laser therapy is a well-tolerated method with possible adverse effects that are usually mild and include dryness as well as itching of the scalp [53].

Microneedling/derma rolling

Microneedling or derma rolling is a complementary treatment modality that is also known as percutaneous collagen induction therapy. It is a widely used method in general dermatology, which has also been incorporated for treating androgenetic alopecia in both men and women. The microneedling procedure involves making micro-punctures of the skin's outer layer by the use of microneedles with a mean length of 0.5–1.5 mm. The exact length of the microneedles as well as the other parameters of therapy such as the most desirable frequency of puncturing, are yet to be discovered and described. Most studies point out that the most effective results may be with the use of needles with a length of 1.0–1.5 mm. However, in one study concerning 60 patients, it was found that microneedling with 0.6 mm needles may be more beneficial than the procedure performed with 1.2 mm needles [54]. When planning the treatment session, it is important to remember to guard the hair follicle bulge area, which resides about 1.0–1.80 mm from the skin surface [55].

There are two types of devices used for performing the procedure at home: a derma roller which is a mechanical roller device and a derma pen which is an electronic pen-shaped device with adjustable speed and penetration depth. The mechanism of action involved in microneedling is based on increasing the release of growth factors on the site of the treated area as well as the activation of stem cells in the hair bulge area. These two processes are thought to increase hair diameter and take part in transforming the vellus hair into the terminal hair. Microneedling is becoming more and more used by dermatologists, as it can enhance the therapeutic effect of treatments like PRP mesotherapy as well as other types of mesotherapies and topical treatments. It is because micro-damages of the skin which are made during the process, increase penetration of the molecules through the skin barrier and therefore the delivery of active substances to the target areas is improved [55, 56].

In the randomized study involving 100 men, a statistically significant increase in the number of hair has been observed within the initial 12 weeks of treatment in the group receiving a combination of microneedling with the needles length of 1.5 mm and 5% minoxidil in comparison to the second group receiving monotherapy with 5% minoxidil [57]. That is why combining topical minoxidil with microneedling may be a way to enhance the effectiveness of topical minoxidil. Patients can perform this procedure on their own. However, it is important to warn them that too deep penetration may lead to the damaging of hair follicles that may further get scarred, as starting with shorter needles and making less pinching repetitions during the initiation, may be appropriate. Microneedling should be performed by the patients once every 14 days (with the use of 1.0–1.5 mm needles). This frequency may be increased when the treatment is being performed with shorter needles (of 0.25 or 0.50 mm) [54].

Anti-androgen therapy

Anti-androgens are used in the treatment of women with hyperandrogenism, which can manifest as acne, excessive hair growth (hirsutism), obesity as well as female pattern hair loss. Some of these medications, like for example spironolactone, may also be used in women affected by androgenetic alopecia, but without coexisting or confirmed hyperandrogenism. Anti-androgens are widely used in dermatology, not only in the management of androgenetic alopecia but also in many other entities such as acne, hidradenitis suppurativa and hirsutism. It is estimated that in 1 out of 3 women, androgenetic alopecia is associated with hyperandrogenism. In these patients, anti-androgenic drugs are often used as the first-line treatment in combination with other drugs, most commonly minoxidil. In men, anti-androgenic drugs are generally not used due to the possibility of triggering the development of feminization symptoms [58].

Spironolactone is probably the most used anti-androgen. Many clinical trials have been showing its efficacy in treating women affected by androgenetic alopecia. Spironolactone acts as an aldosterone receptor antagonist and exhibits hypotensive as well as anti-androgenic effects. The standard treatment protocol for FPHL usually requires starting with 50 mg of spironolactone per day for the first one or two weeks, then the dose is increased to 100 mg per day which accounts for a standard dose that can be finally increased up to 200 mg per day [58, 59]. Spironolactone is often used in conjunction with oral or 5% topical minoxidil, especially when the treatment is

performed with small doses of spironolactone (25–50 mg) [23, 58]. In women, low doses of oral minoxidil (0.25–1.25 mg) are usually a part of the combination therapy. However, one clinical trial has indicated that using the higher doses of oral minoxidil (accounting for 2.5 mg) in conjunction with 25–50 mg of spironolactone, may produce better results in adolescent girls below the age of 18 [60]. The side effects of the treatment with spironolactone are most often related to its diuretic effect and include the following: hyperkalaemia, orthostatic hypotension, frequent urination and weight loss. However, the incidence of hyperkalaemia among women who are treated with spironolactone does not exceed its incidence in the general population of women, which accounts for 0.75%. Electrolyte level changes most commonly happen in women above the age of 45, as it may be important to monitor sodium and potassium serum levels in that particular group of patients. Menstrual disorders can also occur during the treatment with spironolactone in 15–30% of women. Spironolactone should not be prescribed during pregnancy, because of its potential teratogenic effect and just like finasteride and dutasteride, it can cause feminization of the foetal genitals (C category during pregnancy according to FDA) [58, 59]. Oral spironolactone is not used for the treatment of MPHL. However, in clinical trials its topical form is also used in men with many promising results and what is very important, without causing any potential side effects connected with the drug's systemic distribution [61].

The other anti-androgen drug is cyproterone acetate (CPA). Cyproterone acetate can be optionally used in conjunction with other substances such as ethinyl oestradiol. Cyproterone acetate as a very potent anti-androgen, cannot be used in women without coexisting hyperandrogenism. Currently, its use in the treatment of FPHL is being diminished, as it may contribute to the development of CNS meningiomas. The third anti-androgen medication used in the management of FPHL is flutamide. Its oral form is not commonly prescribed as part of AGA management in women. However, a clinical trial from 2022 has shown that flutamide may be very successfully used topically as a 2% solution in conjunction with 5% topical minoxidil [62].

In women of reproductive age that are affected by PCOS, in the management of AGA it is important to use oral contraceptives that exhibit anti-androgenic effects and can further decrease androgens serum levels. Using contraception is also necessary for women who are treated with teratogenic drugs such as finasteride, dutasteride, spironolactone, CPA and flutamide [63].

Hair transplantation

Hair transplantation (HT) has been developed as a surgical treatment of AGA that is performed in both men and women by dermatologists and aesthetic surgeons that are being trained in that area of hair restoration medicine. Typically, the HT modality is used in patients over the age of 25, in case of complete or partial ineffectiveness of pharmacological treatment that does not allow achieving an optimal as well as a satisfactory therapeutic effect. It has been established that the procedure may allow for a long-lasting effect of a natural appearance, which becomes noticeable 6 to 8 months after the surgical procedure, with the final effect appearing around one and a half years after the surgery. It should be noted that approximately 1 to 3 months after the procedure, the telogen phase in the hair cycle of newly transplanted hair begins, as it produces increased effluvium, corresponding to the so-called "ugly duckling stage". This phase then starts to gradually decrease and the site of the treated area becomes naturally hairy and full. What is more, according to the studies, it is estimated that the survival rate of the transplant can reach up to 90%. The procedure is based on the principle of donor dominance, which means that the insensitive to androgens hair follicles that are taken away from the areas in occipital and bitemporal regions retain their properties after being transplanted to the areas that are sensitive to androgens. It can often happen that several surgical procedures are needed to achieve a better and more satisfying result. After the surgery, men in general still require pharmacological treatment, as it does not prevent the progression of the disease on the site that hasn't been covered with the transplanted grafts. It can also happen that the transplanted hair may gradually thin out when they have been previously harvested from the area on the border between the androgen-dependent and the androgen-independent areas. In that case, most men are advised to take oral finasteride. In women, the post-surgery treatment protocol varies depending on the particular case [64, 65].

During the procedure, it is essential to carefully consider the calibre of transplanted hair follicles to determine the density of transplanted hair grafts. In men, when filling the frontotemporal angles and the anterior hairline, it is necessary to ensure the proper angulation of the new hairline and its proper geometry as well, which should be the parameters adjusted to the patient's face. The same practice applies when performing procedures to lower the anterior hairline in women. There are two possibilities for donor follicle extraction: Follicular Unit Transplantation (FUT) and Follicular Unit Extraction (FUE). The FUT technique involves removing a thin strip of the healthy hair-bearing skin and the further extraction of hair follicles by cutting perpendicularly to the axis incision, as it allows for minimizing the incision length as well as bleeding, but also leaves a linear scar that may leave the patient with a negative cosmetic effect, that is usually more visible in patients with short hair. Therefore, this method is more commonly chosen by

women. The FUE technique involves removing groups of 4 hair follicles using a small calibre punch with the help of a robot, which in some cases may leave dispersed white scars up to 1 mm in size, making it more cosmetically acceptable than the traditionally used FUT technique. Additionally, the robot controls the punch angle, which prevents damage to the hair follicles. However, during the clinical studies, it was found that when an experienced surgeon performs the procedure, the frequency of cutting off the hair follicles in both methods is roughly the same and ranges from 5 to 7%. What is more, before performing the FUE transplantation it is necessary to shave a donor area, which may be a problem for some people. Nowadays, the FUE technique is becoming increasingly used as a first-line treatment modality in the surgical management of androgenetic alopecia in men [66].

Oral nutraceuticals

Oral nutraceuticals have been shown to be effective in promoting moderate hair growth in patients with androgenetic alopecia and may serve as a useful supplement to currently available treatments. This group of substances can promote and enhance the effects caused by the standard treatment. Probably, the most examined and well-researched natural nutraceutical would be the saw palmetto (SP) extract, which can be administered systemically as well as topically in the form of shampoo. Saw palmetto acts as the 5α-reductase type I and type II inhibitor that may decrease DHT binding capacity to the scalp AR by up to 50%. Its effectiveness is well documented and that is why SP can be prescribed for the patients unwilling to take finasteride. The standard dose of the medication accounts for 320 mg per day and it may be more effective to split the dosage and take the medication twice daily, as the biological half-life of the SP extract is quite short. The other natural substances that can be used by the patients include melatonin, caffeine, marine extracts, green tea extracts, rosemary oil, pumpkin seed oil and cannabidiol oil [67].

Ketoconazole shampoo

Ketoconazole shampoo is very commonly used for treating severe dandruff, including seborrheic dermatitis. Ketoconazole is an antifungal medication that is derived from imidazole. It exhibits an anti-androgenic activity that is thought to moderately decrease DHT concentration within the scalp and also reduce the excess of sebum production. Therefore, it can be used by patients with androgenetic alopecia as the complementary treatment method in the form of 2% ketoconazole shampoo. It is most advised that the patients use the shampoo 3–4 times a week. However, the adverse effect of such a treatment can be scalp dryness, so it may be important to use moisturizing conditioners to avoid it [11].

Treatment with botulinum toxin type A

The treatment with injections of botulinum toxin type A (BTA) still seems to be more of an experimental method. However, in a trial with 63 patients, it was found that the method may be effective, without causing any serious side effects [68]. The possible explanation of why this method works can be directly derived from the minoxidil's mechanism of action that is associated with the dilation of scalp vasculature. When BTA is administered intramuscularly into the scalp, it causes the relaxation of its muscles, which can further result in decreased pressure on the scalp vessels that enhance the blood flow into the scalp. Therefore, in an oxygen-rich environment, the conversion of testosterone into DHT is less efficient as well as the enzymatic activity of the aromatase is enhanced. It all results in a decreased level of DHT within the scalp, as the miniaturization of hair follicles becomes inhibited.

The treatment with botulinum can be currently performed by some dermatologists, with the promising results of increasing hair growth on the sites that are especially resistant to minoxidil and/or finasteride. That includes the bitemporal area (temples) [68]. The method may become broadly used in the future, however, more trials are needed to thoroughly assess its clinical efficacy.

Ongoing research — what may be broadly used in the future

Currently, probably the most promising and vitally researched new group of medications is the group of topical androgen receptor antagonists, including pyrilutamide, clascoterone and GT20029 [42]. Most research has been already done on clascoterone, as in vitro it provides the same effects as finasteride and was approved by the FDA for the treatment of acne vulgaris. Its mechanism of action is based on the competitive inhibition of the cytoplasmic androgen receptors (AR) [69]. Some specialists may also perform stem cell-based therapies [70]. Mesenchymal stem cells derived from hair follicles and adipose tissue are currently being investigated [71, 72]. Moreover, apart from topical spironolactone and flutamide, topical cetirizine has also been showing some preliminary promising results [42, 73]. Finally, scalp threading with PDO threads may raise the total number of hairs [42].

Apart from that, a very interesting trial has been recently performed with the use of the water extract of *Cacumen platycladi*, which is derived from the tree — *Platycladus orientalis*. In vivo assay, has shown that the high dose of the extract provides the same therapeutic effects as finasteride. These promising results are thought to come from the induction of the Akt/GSK3β/β-catenin signalling pathway, as it promotes hair growth [74]. Many other naturally derived substances are also being thoroughly investigated.

CONCLUSIONS

Androgenetic alopecia is a chronic and persistent disease. Therefore, some authors postulate renaming the condition in women and use the term female pattern hair loss, instead of female androgenetic alopecia. However, the exact character of the disease in women is not yet well-discovered, as both terms are used to describe the same condition. The disease character may vary between individual females, as it is supposedly due to the different aetiology. However, it is a clear fact that some women demand long-lasting treatment, which may also be unlimited. On the other side, androgenetic alopecia in men is a strictly androgen--dependent entity that is chronic and requires the appropriate treatment as long as the patients want to maintain good results. Androgenetic alopecia drastically impairs the quality of life of the affected individuals, making them more prone to the most common affective disorders, including depression and anxiety. Young men in their 20^s and 30^s seem to be especially affected by the burdens of the disease. The standard treatment of androgenetic alopecia involves topical and systemic minoxidil, oral (and possibly topical) finasteride as well as oral dutasteride (with the possibility of its use in mesotherapy). However, the introduction of systemic treatments may be associated with the potential side effects and topical therapies are commonly inaccessible. Many additional pharmacological and nonpharmacological treatment modalities are also available (including the surgical treatment of AGA). There is a great need for further improvement of yet-used modalities, as especially important seems to be properly performed and evaluated follow-up. With the increasing awareness and interest of the patients regarding androgenetic alopecia as well as its widespread in contemporary dermatology, researchers keep on examining the old treatments and also completely new therapies, that base on the main pathoaetiological and molecular mechanisms of androgenetic alopecia, are being discovered. Moreover, the management of patients with androgenetic alopecia should be done by dermatologists with the proper skills and experience in the area of scalp and hair diseases. It is especially important, because nowadays the lack of a single effective treatment and the increased availability of various new drugs in recent years, may be challenging and overwhelming for doctors. Although many therapies are available, choosing the appropriate ones for this chronic condition can be difficult. The other thing is that the efficacy of some of the available treatments may directly depend on the knowledge and experience of the performing doctor.

Article information and declarations

Author contributions

KŚ — conceptualization; methodology; data curation; formal analysis; investigation; resources; validation; visualization; writing: original draft. DS — conceptualization; methodology; data curation; formal analysis; investigation; resources; validation; visualization; writing: original draft. WP — conceptualization; supervision; writing: review and editing. AOS — conceptualization; supervision; writing: review and editing.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

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