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THE USE OF PLATELET-RICH PLASMA IN THE TREATMENT OF ALOPECIA - A REVIEW OF THE LITERATURE

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ABSTRACT

Alopecia is a commonly occurring medical condition. Various types of alopecia are distinguished, with the most common being androgenetic alopecia affecting both men and women. Standard treatments do not always yield the expected results, hence the search for alternative forms of therapy for this condition. Platelet-rich plasma (PRP) has been used in medicine for a long time, but it has gained popularity in aesthetic medicine and dermatology in recent years. The action of PRP includes stimulating collagen formation. The therapeutic effects of PRP therapy in alopecia are achieved through the synergistic action of various types of growth factors.

Aim: The aim of our study was to evaluate the effectiveness of platelet-rich plasma therapy for baldness, to compare its effectiveness with other treatment methods and to present this issue to the reader.

Methods: Analysis of issues related to baldness and platelet-rich plasma therapy from PubMed sources and comparison of the effectiveness of this therapy with other methods.

Conclusions: Treatment with PRP for androgenetic alopecia results in an increase in overall hair density. In chronic plaque alopecia, such therapy leads, among other things, to increased hair regrowth. Combined therapy of PRP with minoxidil in androgenetic alopecia yields better results than using these methods separately. The same applies to combined therapy of PRP with finasteride. However, minoxidil with PRP yields better results than finasteride with PRP.

Keywords: Alopecia, platelet-rich plasma, androgenetic alopecia, exosomes, finasteride, minoxidil

INTRODUCTION

Hair loss is a common dermatological issue that affects both men and women worldwide. This phenomenon not only impacts the patient's appearance but also their mental well-being, emphasizing the importance of treating this condition. There are various subtypes of hair loss, including androgenetic, alopecia areata, seborrheic, telogen effluvium, anagen effluvium, and cicatricial alopecia. The etiopathogenesis of these

types varies, consequently influencing their respective treatments.

Currently, numerous studies are focusing on the potential utilization of platelet-rich plasma (PRP) therapy in the treatment of hair loss. This work primarily concentrates on exploring the possibilities of using PRP in individual types of hair loss and analyzing the effectiveness of such therapy in comparison to other therapeutic options.

The objective of our study was to provide a detailed overview of this issue, thoroughly analyze and present the effectiveness of PRP therapy, and acquaint the reader with therapeutic possibilities and the latest findings in this field.

METHODS

We meticulously analyzed the medical literature concerning hair loss, platelet-rich plasma, and the potential treatment of this condition with platelet-rich plasma (PRP). The materials for our analysis were sourced from the PubMed database. Subsequently, we compared the effectiveness of using PRP with other methods of treating hair loss.

HAIR LIFE CYCLE

The processes involved in the life cycle of the hair and its growth and formation of the hair follicle are coordinated and extremely complex, and depend on the interplay of various signals and stimuli. The hair follicle is a highly ordered epithelial structure that undergoes cyclic modifications during morphogenesis. On average, each of us has about 100 thousands of hair on the scalp in various stages of the growth cycle, with the average lifespan of a hair shaft being 3.5 years. Its monthly growth is estimated at about 1.25mm. [1] It is also worth mentioning that on average we lose about 100 hairs every day. We can divide the hair growth cycle into 3 basic phases: anagen, catagen, telogen. In the anagen phase, which is the active phase of hair growth, there are about 84% of hair on the scalp. It is characterized by significant cell proliferation. This phase lasts an average of 2 to 7 years, and it is when the hair follicle reaches its maximum volume and length [1] This phase involves the final differentiation and epithelial growth of the hair follicle into the dermis with matrix regeneration and hair shaft formation. [2] The involution phase, or catagen, which lasts 2-4 weeks, contains about 1-2% of hair. Control of this phase is highly significant, as ending anagen too early contributes to conditions such as hair loss and various types of alopecia, while prolonged catagen can cause hirsutism. [3] Insulin-like growth factor-1 (IGF-1), hepatic growth factor (HGF) and vascular endothelial growth factor (VEGF) are said to be important factors for maintaining anagen. [4] This phase is followed by telogen, or relative resting phase, which lasts about 3 months, during which reduced proliferative activity of the hair follicle is observed. It is estimated that 10-15% of hair remains in this phase. [1]

TYPES OF HAIR LOSS:

Alopecia is a symptom that can be a result of several conditions that are both local and systemic in nature. Depending on the presence of inflammation and destruction of hair follicles, the distinction between two types of alopecia: scarring (cicatrical) and non-scarring (non-cicatrical) arises.

Non-scarring alopecia manifests itself with hair loss within the non-inflamed scalp and results from impaired hair growth, abnormal length of hair cycle phases or chronic mechanical damage to the hair. The group of non-scarring alopecia includes: androgenetic alopecia, alopecia areata, telogen effluvium, anagen effluvium, traction alopecia and trichotillomania.

Scarring alopecia affects the hair follicles, leading to their damage, atrophy and replacement by connective tissue. Scarring alopecias can be further classified as primary and secondary. The term primary scarring alopecia describes a process that directly damages the hair follicles and contains entities like lichen planopilaris, frontal fibrosing alopecia, discoid lupus erythematosus, folliculitis decalvans, central centrifugal cicatricial alopecia or acne keloidalis. Secondary scarring alopecia, on the other hand, primarily affects the dermis and the hair follicles are affected secondarily. Causes of secondary cicatricial alopecia include scleroderma, pemphigoid, neoplasms, chemical and physical agents, bacterial or fungal infections. [5]

Androgenetic alopecia (AGA) accounts for 37.7% of all alopecia cases and is the most common cause of chronic hair loss in the world population. [6] The disease can affect both men and women but due to the different patterns of hair loss in both sexes, we distinguish between male and female pattern alopecia. AGA is characterized by miniaturization of hair follicles and shortening of the anagen phase, which is caused by hypersensitivity of hair follicles to androgens, especially to dihydrotestosterone (DHT) in genetically predisposed individuals. [7] Male pattern hair loss begins at the frontal angles and the vertex, progresses gradually over the years and can lead to complete baldness of affected areas. Typically, hair in the occipital and temporal regions are spared due to their lower sensitivity to DHT. [8]

On the other hand female pattern hair loss presents as diffuse thinning vertex region, gradually spreading

bilaterally in the temporal directions but with frontal hairline usually intact. There is rarely a complete loss of hair of the involved areas, but rather a reduction in hair density. [9] Some researchers classify female pattern hair loss as a separate entity. [10]

Telogen effluvium (TE) is characterized by diffuse hair loss within the non-inflamed scalp. It accounts for 11.3% of alopecia cases. [6] TE is a result of shortening of the anagen phase and an increase in the percentage of telogen hair >25% in response to a stressor to the organism such as severe infection, extensive surgery, childbirth, significant weight loss, certain medications - most commonly retinoids, anticoagulants (heparins), anticonvulsants, antithyroid drugs. The causative agent cannot be identified in about 1/3 of the cases. [11,12] Massive hair loss begins 2-3 months after exposure to the stress factor, and if it is a one-time event, after 3-6 months the changes in the length of hair cycles normalize and gradual hair regrowth occurs. [13]

Alopecia areata (AA) manifests as hair loss in regular, circular, well-demarcated foci on the scalp, but can also affect the eyebrows, armpits and pubic area. Severe form leads to complete baldness of the scalp (alopecia totalis) or even the entire body hair (alopecia universalis). The course of AA is unpredictable, some patients experience only one episode of hair loss, while in other cases the disease remits and relapses over the years.(14) AA occurs with a frequency of about 0.1-0.2% and accounts for 18.2% of all alopecia cases. [6,15] The pathogenesis is autoimmune, most likely a lymphocyte T mediated damage to the hair follicles but occurring without apparent signs of inflammation.[16] AA coexists with other autoimmune conditions such as vitiligo, Hashimoto's thyroiditis and type 1 diabetes [17].

Lichen planopilaris (LPP) is an autoimmune disease that is also caused by perifollicular inflammation mediated by Th lymphocytes but resulting in irreversible damage to the hair follicles. The disease predominantly affects women in the age 40-60, men are affected less frequently, occasionally it is described in children. LPP manifests as hair loss of the vertex, but any area of the scalp can be affected. The lesion expands with visible inflammation especially on its edges and is accompanied by pain, itching, redness, tenderness and hyperkeratosis . [18] Frontal fibrosing alopecia (FFA) is a variant of LPP that causes a symmetric band-like alopecia of the frontal and temporal regions leading to recession of the hairline, and often affecting the eyebrows. [5,19] Together LPP and FFA account for 18.4% of all alopecia cases and are the most common cause of scarring alopecia. [6]

PLATELET-RICH PLASMA - BASIC INFORMATION

Platelet-rich plasma (PRP) is an autologous blood product that has an increased concentration of platelets, above physiological levels. It is obtained from the patient's whole blood, which is then centrifuged.[20,21] The concentration of platelets is 2 to 3 times higher than in peripheral blood. (23) Platelet-rich plasma is obtained from the same patient, so there is no risk of transmission of infectious diseases such as hepatitis B and C or AIDS. [24]

The term platelet-rich plasma (PRP) began to be used in the 1970s. At the time, hepatologists used PRP for transfusions in patients with thrombocytopenia. (20) Interest in PRP has continued to grow in many fields. Platelet-rich plasma began to be used in regenerative medicine, initially in dental and maxillofacial surgery. PRP has regenerative effects on skeletal and connective tissues in maxillofacial or periodontal diseases. PRP's therapeutic effect on cartilage, tendons and muscles began to be used in orthopedic surgery, in tissue regeneration after sports injury. PRP has been effective in relieving the symptoms of certain tendon injuries. [23] PRP has also been used in plastic surgery, pediatric surgery, cardiac surgery, gynecology, urology and ophthalmology [24] and the treatment of diabetic foot ulceration. [23] Recently, there has been an increased interest in PRP in dermatology and aesthetic medicine, where PRP is used in wound healing, skin rejuvenation, alopecia, and burn healing. [21] PRP, thanks to its ability to activate fibroblasts and stimulate collagen synthesis, is used in improving post-surgical and acne scars. (23)

Platelets, also known as thrombocytes, are a component of the blood. They are formed in the bone marrow. They take part in hemostasis through adhesion, activation and aggregation. They respond to bleeding from a damaged vessel by accumulating at the site of an endothelial break. They become activated, and their granules release factors that promote clotting. Platelets join together to form a platelet plug. [21] Thrombocytes contain growth factors, cytokines, chemokines and cell adhesion molecules. They affect cell proliferation, angiogenesis, chemotaxis, stem cell migration, and can alter the mechanism of immune response and the mechanism of inflammation. [22,23]

PRP preparation begins with the collection of whole blood by puncturing the patient's vein. [22] The blood is collected into anticoagulated tubes (acid citrate or sodium citrate). The blood is then centrifuged using a centrifuge at the speed specified by the manufacturer. A number of PRP systems approved by the Food and Drug Administration and Health Canada are available for use. [23] Differential centrifugation is used to prepare PRP. Each component of whole blood has a different specific gravity, so after centrifugation it is separated into different layers. The centrifugation process is carried out in one or two stages. [20] After the first centrifugation step, three layers are produced: red blood cells (RBCs) at the bottom, platelet-poor plasma (PPP) in the supernatant and a 'buffy coat' (BC) layer rich in leukocytes and platelets in between.

The second step varies according to many protocols. [25] To produce pure PRP (P-PRP), the PPP and platelet top layer of BC are transferred to another tube for another centrifugation and the RBC value is discarded. Most of the PPP layer is then discarded. P-PRP consists of the superficial part of the BC (containing a lot of platelets) suspended in fibrin-rich plasma. Most of the leukocytes are then discarded. [25] In order to produce leukocyte-rich PRP (L-PRP), PPP, the full layer of BC together with a small number of red cells from underneath are transferred to another tube for another centrifugation. The PPP is discarded. The final L-PRP consists of the entire BC layer, which contains the majority of platelets and leukocytes and a minimal number of RBCs suspended in fibrin-rich plasma. [25] The preparation of PRP is very important as it directly affects the final composition of PRP. The transfer of PPP and BC is most often performed manually with a syringe or pipette using only vision. [25] When this is the case, the final composition of PRP is not completely determined and there may be differences in the levels of WBCs and RBCs.[20] Collins et al [20] concluded that future standardisation of parameters for future PRP studies is needed to provide robust evidence. [20]

There are currently a number of PRP preparations available. In order to determine the optimal preparations for specific pathologies, several authors have attempted to classify PRP preparations. However, each classification has considered new and additional factors. [20] The first division was presented by Ehrenfest et al [25], who classified the preparations according to leukocyte content and fibrin network density. They divided PRP preparations into:

- Pure platelet-rich plasma (P-PRP) - leukocyte-poor, low-density fibrin network
- Leukocyte and platelet-rich plasma (L-PRP) - contains leukocytes, low-density fibrin network
- Pure platelet-rich fibrin (P-PRF) - without leukocytes, high-density fibrin network
- Leukocyte and platelet-rich fibrin (L-PRF) - contains leukocytes, high-density fibrin network

Pure platelet-rich plasma (P-PRP) can be rapidly injected. Leukocyte and platelet-rich plasma (L-PRP), like fibrin glue, can be placed on skin wounds and sutures to accelerate healing. Pure platelet-rich fibrin (P-PRF) as well as leukocyte and platelet-rich fibrin (L-PRF) cannot be injected, due to the strong fibrin matrix. [23] Gupta et al [23] concluded that there is a lack of scientific studies comparing the therapeutic efficacy of different PRP systems for different conditions and the need for more multicentre, randomised trials. They pointed out that the long-term side effects of PRP use in many areas of medicine are unknown.[23]

ALOPECIA THERAPY WITH PLATELET-RICH PLASMA

Platelet-rich plasma contains high concentrations of growth factors (GFs) [26, 27,28,29,30,31], released from α-granules of platelets by degranulation [29,31,32]. Growth factors released from platelets include platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), transforming growth factor (TGF-β) and insulin-like growth factor 1 (IGF-1) [21,26, 27,28,29,30,31]. The effectiveness of PRP therapy in alopecia is due to the synergistic action of multiple growth factors.

The mechanism of action of growth factors present in platelet-rich plasma (PRP) includes stimulation of proliferation and differentiation of cells surrounding the hair bulb [21,26,27,33,34]. In addition, they promote the process of angiogenesis, which results in increased vascularization of the hair follicle, while promoting the delivery of nutrients and oxygen to the area [21,26,34,35]. PRP growth factors, through activation of the ERK/Akt and Wnt/B-catenin signaling pathway, influence the induction and prolongation of the anagen phase of the hair growth cycle [21,27,29,31,34,35,36]. Activation of the Akt signaling pathway counteracts the degradation of Bcl-2 protein, which exhibits anti-apoptotic properties [21,29,31,36].

In contrast, activation of the Wnt signaling pathway leads to the accumulation of B-catenin, which promotes proliferation and differentiation of hair follicle stem cells and angiogenesis [21,26,31].

Alves et al. conducted a randomized double-blind study to evaluate the efficacy of androgenetic alopecia therapy using platelet-rich plasma. Twenty-five patients with androgenetic alopecia, both male and female, participated in the study. The scalp areas were divided into two halves. One-half of the scalp was injected with platelet-rich plasma, while the other half was injected with saline solution (placebo). After 3 and 6 months of treatment, statistically significant improvements in the mean number of anagen hair, telogen hair, hair density and terminal hair density were observed, compared to baseline values. Compared to the control group, only a statistically significant increase in mean total hair density was observed on the side treated with platelet-rich plasma (PRP) [37].

A meta-analysis conducted by Gupta et al. to evaluate the efficacy of platelet-rich plasma (PRP) therapy in the context of androgenetic alopecia analyzed patient hair density [38,39]. A statistically significant increase in hair density was observed, compared to baseline values and to a control group that received a placebo in the form of a saline solution [39].

A one-year randomized double-blind study by Trink et al [40] examined the effect of platelet-rich plasma (PRP) in 45 patients with chronic alopecia areata AA. Compared to the control group, a significant increase in hair regrowth was observed, at the same time there was a decrease in the number of dystrophic hairs and a significant increase in the level of Ki-67 (40,41), an indicator of cellular proliferation [31].

Despite the numerous publications on the efficacy of platelet-rich plasma therapy for alopecia, it would make sense to conduct extensive and more controlled clinical trials involving a broader group of patients [29,34,42,43]. In this context, simultaneous standardization of the sample preparation process is crucial [34,42]. Failure to standardize the manufacturing procedure leads to samples with varying compositions of platelets, leukocytes, erythrocytes and growth factors, which can result in differential therapeutic effects [44].

OTHER THERAPIES FOR ANDROGENETIC ALOPECIA AND COMPARISON OF THEIR EFFECTS WITH PLATELET-RICH PLASMA

Androgenetic alopecia as mentioned is the most common type of alopecia affecting both men and women. It is progressive and if left untreated leads to progressive hair loss and thus has a negative impact on mental health [45]. Genetic background plays a very important factor in the development of the condition; however, environmental factors can trigger or exacerbate the problem. Androgen-influencing factors such as progestin-containing contraceptive drugs or hormone replacement therapy can be a factor in intensifying androgenetic alopecia. Therefore, the primary method of treatment is to stop using the agents that cause the problem [46].

Pharmacological treatments for androgenetic alopecia have included minoxidil, finasteride, dutasteride, photobiomodulation, hair transplantation, microneedling, PRP and exosomes [47].

Minoxidil originally found use as an oral medication for hypertension. Its side effect was to stimulate hair growth in patients. This effect was used for the topical treatment of alopecia. Today, minoxidil is available as a 5% or 2% solution, which is applied topically. The mechanism of the drug's action on hair growth is not definitively understood, but the main role of the drug's action is attributed to its metabolite minoxidil sulphate [48]. There are 2 types of phenol sulphotransferases in the scalp, which are responsible for the formation of the aforementioned metabolite. Patients with higher enzyme activity responded better with hair growth than patients with lower enzyme activity. Goren et al. found that the use for 14 days, low doses of aspirin and salicylates reduced the enzymatic activity of phenol sulphotransferases contained in the hair follicles and thus reduced the therapeutic values of minoxidil [49].

Another theory is that minoxidil affects the opening of potassium channels, which play an important role in the cell cycle, leading to increased DNA production and increased cellular proliferation within the hair follicles [48]. Minoxidil is likely to have an effect on prolonging the anagen phase of the hair and shortening the telogen phase [48]. Minoxidil may also owe its efficacy in the treatment of androgenetic alopecia to a potential anti-androgenic effect. It has shown an effect of reducing the expression of the 5-alpha-reductase type 2 gene in keratocyte cells. However, these results require further study [50]. A meta-analysis by Adil et al. indicates the efficacy of minoxidil relative to the study group versus placebo. Additionally, the use of minoxidil at a concentration of 5% twice daily increased the number of hairs per cm2 relative to a concentration of 2% [45].

Minoxidil therapy can be a combination therapy with micro-punctures and PRP. A study on a group of 50 patients with androgenetic alopecia showed a better effect of topical minoxidil with PRP than treatment with topical minoxidil alone. (51).

Finasteride is a cometic inhibitor of steroid 5-alpha-reductase types 1 and 2, with a much higher affinity for type 2 reductase. [52] This enzyme is key to catalysing the reaction of dihydrotestosterone (DHT) formation from testosterone. The effect of the drug is to reduce the concentration of DHT in the body and thus reduce the activity of androgen receptors in the prostate and scalp [53]. The effect on the prostate found application in the 1990s for the treatment of benign prostatic hyperplasia. In 1997, finasteride was approved for the treatment of androgenetic alopecia [54]. The therapeutic dose is 1mg/day by oral route. A randomised phase 3 clinical trial of topical finasteride showed a significant improvement in androgenetic alopecia relative to a placebo trial, and determined an effect level similar to orally taken finasteride with a lower effect on serum DHT levels [55]. The effect of finasteride on androgenetic alopecia is confirmed in studies. A Japanese study involving 3,000 men with androgenetic alopecia showed over a three-year period significant hair regrowth in 11%, moderate hair regrowth in 36.5% and slight hair regrowth in 39.5% [56].

Finasteride has also been shown to have a therapeutic effect on androgenetic alopecia in women, however, due to the increased risk of birth defects in male children, it is not recommended and minoxidil remains the pharmacological treatment of first choice [57,58].

An important aspect of finasteride use is the side effects it causes. These include decreased libido, erectile dysfunction, ejaculatory dysfunction, testicular atrophy, hypogonadism, gynaecomastia and increased risk of

breast cancer in both men and women. The most vulnerable group are those with Klineferter's syndrome, whose risk is 50 times that of a healthy person [52,53]. Of concern are reports of Post-finasteride syndrome, which has been reported in people who have stopped taking finasteride. Symptoms related to decreased libido, erectile dysfunction and sexual dysfunction lasted up to 16 months after discontinuation of the drug. Additional symptoms included gynaecomastia, brain fog, increased anxiety and suicidal thoughts. The mechanism of post-finasteride syndrome is explained by the blocking of catalysing 5-alpha-reductase reactions contained in various human organs. This results into a multifaceted disruption of neuroactive steroids. [59]

Combination therapy of finasteride with PRP has a more beneficial effect than the use of 1mg/day finasteride alone. However, comparison of PRP with minoxidil 5% and PRP with finasteride shows a total mean hair count change of 9.8 ± 26.9 hairs versus 0.6 ± 10.8 hairs. Combination therapy of PRP with minoxidil 5% showed better parameters in mean hair count, hair density, anagen and telogen percentages than PRP with finasteride 1mg/day [60].

Dutasteride, like finasteride, is also a selective and competitive 5-alpha-reductase inhibitor, but it has a high affinity for both type 1 and type 2 of enzyme. The mechanism of action is similar to that of finasteride described earlier. The effects of dutasteride are superior to those of finasteride in the treatment of androgenetic alopecia. The incidence of adverse effects of both drugs is similar [61,62].

Exosomes are vesicles surrounded by a lipid bilayer containing bioactive lipids, proteins, DNA, mRNA, tRNA and other biologically active proteins needed for repair, and regeneration of cells and tissues. Exosomes arise from stem cells and function as communication between cells both near and far. They generate the appropriate cellular response. It is suggested that exosomes carry Wnt proteins that induce beta-catenin activation at a distance. This pathway, as mentioned earlier, is important for hair regeneration and morphogenesis. Studies indicate that exosomes may represent a revolution in the treatment of alopecia [63,64].

There are no studies to compare the efficacy of exosomes and PRP. However, the cost of exosomes treatments is significantly higher than PRP treatments [65].

CONCLUSIONS

Platelet-rich plasma (PRP) therapy is effective in treating androgenetic alopecia as well as chronic plaque alopecia as a standalone treatment. Furthermore, PRP used in conjunction with minoxidil or finasteride yields better results than when these preparations are used separately. The best outcomes are achieved with combined therapy of minoxidil and PRP. Standardization of the PRP preparation process is necessary to achieve the best and safest results.

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