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Special Topic

Platelet-Rich Plasma and Stem Cells for Hair Growth: A Review of the Literature

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Abstract

The prevalence of hair loss, its psychological consequences, and historically subpar treatments present a unique challenge to the physician. The current Food and Drug Administration–approved treatments for hair loss are plagued by ineffectiveness, noncompliance, and adverse effects. Recent advances in our understanding of hair physiology have fueled the development of more efficacious, minimally invasive, and safer treatment options for hair restoration including plasma-rich protein and stem cell therapy. Platelet-rich plasma, the autologous preparation of concentrated platelets in plasma, when injected into the scalp of patients with both androgenetic alopecia (AGA) and alopecia areata (AA), has been shown to increase hair count and density. The clinical findings have been supported by histologic evaluation of the scalp skin. These findings have been recapitulated in numerous randomized controlled trials. Stem cell therapy, although newer in its application in hair restoration, has also been effective for treating both AGA and AA. The isolation techniques for stem cells are varied, but regardless have shown promising results in early prospective and retrospective studies.

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Hair loss is a common condition encountered in dermatologic practice. Although considered a medically mild problem, hair loss has well-documented psychosocial consequences, especially in women.[1,2] Given its prevalence and associated impact, it is no surprise that the hair-loss industry earns close to $4 billion annually in the United States.

Androgenetic alopecia (AGA) is the most common type of hair loss, affecting up to 50% of males between the ages of 40 and 49.[2] Despite its prevalence, minoxidil and finasteride are the only Food and Drug Administration–approved treatments for AGA, and their use and efficacy are often compromised due to noncompliance and adverse effects. Hair restoration surgery presents another more permanent solution, but the cost is prohibitive for many, and the invasive nature of the surgery required is offputting for many potential patients.

The prevalence of hair loss, its psychological consequences, and historically subpar treatments present a unique challenge to the physician. In recent years, enhanced understanding of the pathophysiology of hair growth has led to the development of more efficacious and safer treatment options.

In this article, we review the use of platelet-rich plasma (PRP) and stem cell therapy to treat various types of alopecia. The PubMed database was searched (N.S.) for studies published between January 2014 and December 2018 regarding the use of PRP in alopecia. The literature search was conducted in January 2019, and involved the following terms: ("PRP" OR "platelet rich plasma") AND ("alopecia" OR "androgenetic alopecia" OR "AGA" OR alopecia areata" OR "AA" OR "hair loss"). Papers published in English that compared the efficacy of PRP as a hair-loss treatment with either baseline or controls were included. In addition, references from identified publications were

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reviewed for any further studies that may be relevant to the literature review. The search results were reviewed by S.K.

PLATELET-RICH PLASMA

Introduction

PRP, the autologous preparation of concentrated platelets in plasma, is a remarkable technique in regenerative medicine. Many specialties have adapted its use for a variety of medical applications including musculoskeletal injuries, wound healing, hemostasis, scar revision, skin rejuvenation, and more recently alopecia.

Mechanism of Action

The mechanisms by which PRP exerts its regenerative effects rely on the degranulation of platelet α granules which leads to the release of a numerous cytokines, including platelet-derived growth factor (PDGF), transforming growth factor (TGF), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), and interleukin 1 (IL-1).[3] These proteins result in a myriad of downstream consequences including hemostasis, inflammation, angiogenesis, and stem cell migration and proliferation.[4]

With regards to hair growth, the contents of the platelet α granules stimulate propagation and signaling among stem cells in the follicular bulge area and among mesenchymal-derived germinative cells of the dermal papilla. This increase in the number of follicular bulge and dermal papilla cells from baseline was observed histologically in PRP-treated scalp skin.[3,5] These actions ultimately stimulate the development of new follicles and activate the proliferative anagen phase of hair growth.[6,7]

A number of cytokines released from the α granules also stimulate hair growth through the promotion of angiogenesis. VEGF, naturally secreted by the keratinocytes of the outer root sheath and the fibroblasts of the dermal papilla, is a known mediator of angiogenesis via endothelial cell proliferation. The increase in the perifollicular vascular plexus around the hair follicle and subsequent improvement in cutaneous ischemic conditions is observed histologically in PRP-treated skin compared with baseline.[5,8] These effects promote hair growth and increase hair follicle and shaft size.

The molecular pathways by which PRP promotes cell proliferation, differentiation, and hair growth were elucidated by Li et al[3] in a number of in vitro studies of cultured dermal papilla cells. PRP treatments were found to upregulate β-catenin and fibroblast growth factor 7 (FGF-7) expression in the dermal papilla cells compared with controls; these proteins are essential for prolonging the anagen phase, delaying progression into the catagen phase, as well as differentiation of stem cells into hair follicle cells.[3] The evidence that PRP prolongs the anagen phase of the hair cycle is supported clinically in a number of studies that demonstrate higher anagen/telogen ratios in areas treated with PRP than in control areas treated with saline injections.[4] The investigators found that PRP treatments also increased expression of Akt and Bcl-2 in cultured dermal papilla cells.[3] Akt is known to upregulate B-cell lymphoma-2 (Bcl-2) directly through the phosphorylation of cyclic AMP response element binding protein (CREB), as well as indirectly through the inhibition of glycogen synthetase kinase-2 β (GSK3B), which normally promotes the degradation of Bcl-2.[9] The culmination of these pathways prevents apoptosis and promotes cell survival, ultimately leading to cell growth and prolonged survival of hair follicles.

Technique

The preparation of PRP relies on the differential centrifugation of whole blood, a process that separates the cellular constituents based on their specific gravity. Autologous blood is first collected from the patient via venipuncture into tubes that contain an anticoagulant such as acid citrate dextrose or sodium citrate solution. The blood is then spun per settings established by the manufacturer resulting in the separation of blood into 3 basic layers: red blood cells, leukocytes, and platelets. The platelet layer, which is the least dense and thus lies on top, is further separated into PRP and platelet-poor plasma (PPP). In vivo, platelets are inert unless "activated" by endothelial damage or subendothelial collagen exposure. In many protocols, PRP is similarly activated prior to injection with thrombin or calcium chloride to promote the degranulation and activation of platelets.

Given the differences in equipment, centrifugation forces, number and length of centrifugation cycles, activation of platelets, and the ultimate composition of PRP, it remains unclear what protocol produces the optimal PRP preparation for hair restoration. Even the frequency of treatments and areas of treatment have yet to be standardized. Each variable must be considered separately in order to establish a successful standardized protocol.

The efficacy of PRP was initially thought to rely mostly on the platelet increase factor—the platelet concentration increase in PRP compared with whole blood. The physiologic count of platelets circulating in the blood stream ranges from 150,000 to 400,000 platelets/μL.[4] In general, the best hair restoration results seem to be attained with platelet concentrations 3 to 5 times that in whole blood.

That being said, whole blood contains a number of cells in addition to platelets, including red blood cells and leukocytes, that affect hair growth and must be taken into consideration. Red blood cells are a source of reactive oxygen species that are theoretically detrimental to the hair growth cycle. Similarly, leukocytes injected at the depth of the hair follicle could worsen hair loss by mimicking the pathology of inflammatory alopecias. Thus, preparations of PRP are distinguished based on their concentration of leukocytes—leukocyte-poor PRP (pure PRP) contains a concentration of leukocytes lower than that of whole blood, whereas leukocyte-rich PRP (L-PRP) contains a concentration of leukocytes higher than that of whole blood.[10–12]

The DEPA classification proposed by Magalon et al[11] considers a number of novel factors to standardize PRP preparations. The DEPA classification is based on the ***d***ose of injected platelets, the ***e***fficiency of production, the ***p***urity of the PRP obtained, and the ***a***ctivation of the PRP. The dose of injected platelets is calculated by multiplying the platelet concentration in PRP by the volume of PRP obtained, and theoretically corresponds to the quantity of platelets and thus growth factors delivered to each injection site.[11] The efficiency of production reflects the percentage of platelets collected from whole blood and relies on the device used; device efficiencies range from >90% recovery rate to <30% recovery rate. The recovery rates reported in the literature vary from 13.1% (Selphyl Device, Cascade Medical Enterprises, LLC, Wayne, NJ) to 79.3% (RegenLab, Le Mont-sur-Lausanne, Switzerland).[11,13,14] PRP purity is based on the overall composition of the PRP; a very pure preparation is considered to have >90% platelets as compared to leukocytes and red blood cells. Lastly, the activators, such as autologous thrombin or calcium chloride, are taken into account.[11]

A number of studies investigating the efficacy of PRP for treating AGA have been published and are outlined below. The outcomes are promising although the methods are highly varied. Very few head-to-head trials comparing PRP preparations and protocols have been published. Hausauer and Jones[15] conducted a randomized trial to investigate a superior protocol for PRP. Forty patients were randomly assigned to 1 of 2 treatment groups: the first group received 3 monthly PRP treatments with a booster session 3 months later; the second group received 2 PRP treatments spaced 3 months apart. Although both treatment groups achieved a statistically significant increase in mean hair count at 6 months compared with baseline, the first group demonstrated a statistically significant increase in mean hair count at 3 months, greater absolute and percentage change from baseline, as well as higher satisfaction rates compared with the second group. Based on these results, the authors suggest that monthly treatments upon initiation therapy provide earlier and more clinically relevant hair regrowth.

Applications in Androgenetic Alopecia

AGA is the most common cause of hair loss worldwide and is characterized by progressive hair loss secondary to a shorter anagen phase, progressive hair follicle miniaturization, as well as perifollicular inflammation and subsequent fibrosis.[16] Dihydrotestosterone (DHT), an androgen produced from testosterone via type II 5-α reductase, as well as chronic inflammation, have been implicated in the pathogenesis of AGA.[17]

In 2006, Uebel et al[6] were the first to demonstrate the positive effects of PRP on hair growth after increased hair growth and density were noted with PRP-treated follicular units used for hair transplantation. Since then, a plethora of randomized controlled trials have been published regarding PRP and AGA (Table 1), albeit with variability in study design and quantification of outcomes.[5,15,18-25]

The first randomized, placebo-controlled trials were conducted in males with AGA. Both used half-head study designs in which half the scalp was injected with PRP and the other half with saline. Injections were performed monthly for a total of 3 sessions.[5,18] Both studies demonstrated beneficial effects with significant increase in mean hair count and density in PRP-treated areas of the scalp.[5,18] Gentile et al[5] followed the participants for 2 years—one of the longest follow-up periods in the literature—and relapse was not noted until 12 months after the last treatment. Histologic findings mirrored the clinical benefits with significant increases in epidermis thickness, number of hair follicles, and Ki67+ basal keratinocytes of epidermis and hair follicular bulge cells observed in PRP-treated skin compared with baseline.[18]

Gentile et al[19] repeated a randomized, half-head study in 18 patients with AGA, but used nonactivated preparations of PRP produced with the CPunT Preparation System (Biomed Device, Modena, Italy) instead of activated preparations. Results mirrored earlier studies with significant increases in hair count and total hair density when compared with baseline and the control side. Histologic sections showed similar changes as described in their earlier studies—increased epidermal thickness, Ki67+ keratinocytes, number of follicles, follicular bulge cells, and vascularization relative to baseline.

Alves and Grimalt[20] conducted a randomized, double-blind, placebo-controlled study involving 25 patients with AGA utilizing a similar protocol—3 monthly sessions of PRP injections into half of the scalp and saline injections into the other half. At both the 3- and 6-month follow-ups, the treatment side demonstrated a significant increase in the mean anagen hairs, telogen hairs, hair density, and terminal hair density compared with baseline.[20] They also reported a significant correlation between mean total hair density and male sex, patients aged ≤40 years, beginning of hair loss at ≥25 years of age, positive family history, and

Table 1. Randomized Controlled Trials Evaluating the Effects of PRP in AGA

Study, year	No. of patients	Treatment	Outcomes
Alves, 2016[20]	25 (13 F, 12 M) 22 completed (11 F, 11 M)	Three monthly PRP treatments injected into half of scalp, saline injections into the contralateral scalp	• Increase in mean anagen hairs, telogen hairs, hair density, and terminal hair density at 3 and 6 months in PRP-treated scalp compared with baseline • Increase in hair density in PRP-treated scalp compared with control side at 3 and 6 months
Cervelli, 2014[18]	10 M	Three monthly PRP treatments injected into half of scalp, saline injections into the contralateral scalp	• Increase in hair count and density in PRP injected scalp when compared to baseline and control side at 3 months • Increase in epidermal thickness, number of hair follicles, Ki67+ basal keratinocytes and blood vessels around hair follicles on microscopic exam of treated scalp compared to baseline
Gentile, 2015[5]	23 M	Three monthly PRP treatments injected into half of scalp, saline injections into the contralateral scalp	• Increase in hair count, hair density, and terminal hair density in PRP-injected scalp when compared with baseline and control side at 3 months • Increase in epidermal thickness, number of follicles, Ki67+ basal keratinocytes, and blood vessels around hair follicles on microscopic examination of treated scalp compared with baseline
Gentile, 2017[19]	24	• Eighteen participants received 3 monthly nonactivated PRP treatments injected into half the scalp and saline injected into contralateral scalp • Six participants randomly assigned to receive a single treatment of calcium-activated PRP prepared by 1 of 2 different systems	• Increase in number of hair counts and hair density in area treated with nonactivated PRP when compared with control area by TrichoScan (Tricolog GmbH, Freiburg, Germany) analysis at 3 months • Increase in epidermal thickness, number of follicles, Ki67+ basal keratinocytes, and improved vascularization on microscopic examination of nonactivated PRP-treated scalp compared with baseline at 3 months • Increase in hair density and follicular unit density in subjects receiving PRP generated from the Arthex Angel System at 6 months compared with baseline
Hausauer, 2018[15]	40 (30 M, 10 F) 39 completed (29 M and 10 F)	Subjects randomly assigned into 2 groups: • Group 1: 3 monthly PRP treatments with booster treatment after 3 months • Group 2: 2 PRP treatments spaced 3 months apart	• Significant increase in hair count at 3 months seen in group 1 compared with baseline • Significant increase in hair count in both groups at 6 months compared with baseline • Significantly higher mean percentage change in group 1 compared with group 2 at 6 months • Increase in hair shaft caliber in both groups at 3 and 6 months when compared with baseline (no significant difference between treatment groups) • Satisfaction scores higher in group 1 than in group 2
Kachhawa, 2017[24]	50 M (44 completed)	Six PRP treatments separated by 21 days injected into the androgen-related areas of the left scalp, saline injections into androgen-related areas on of the right scalp	Increase in overall hair density, quality, and thickness noted in images and on trichoscopy after treatment in left side of scalp compared with baseline
Mapar, 2016[23]	19 M (17 completed)	Two 2.5 cm × 2.5 cm square areas at least 3 cm apart on the scalp chosen; 1 spot injected with PRP and 1 with saline; 2 injections 1 month apart	No change in terminal hair count or vellus hair count in the experimental square compared with the control square at 6 months
Puig, 2016[22]	26 F	Subjects randomly assigned to receive either 1 treatment of PRP or 1 injection of saline into the central scalp	• No statistical difference in hair count or hair mass index between experimental and control groups • More subjects in experimental group reported substantial improvement in hair loss, rate of hair loss, hair thickness, ease of managing hair, and coarser/heavier hair
Rodrigues, 2018[25]	26	Subjects randomly assigned to receive either 4 treatments PRP or saline injections every 15 days	• Increase in hair count, density, and percentage of anagen hairs in PRP group compared with control and baseline after treatment • No change in terminal/vellus hair ratio between the PRP and control group
Tawfik, 2018[21]	30 F	Four weekly PRP treatments injected into select area of scalp, saline injected into another selected area of the scalp	• Increase in hair density and thickness in PRP-treated area compared with control area and baseline by physician assessment of photographs and folliscope at 6 months • Decrease in number of subjects with positive pull test in the PRP-treated area compared with control area at 6 months

AGA, androgenetic alopecia; F, females; M, males; PRP, platelet-rich plasma.

Table 2. Prospective Cohort Studies Evaluating the Effects of PRP in AGA

Study, year	No. of patients	Treatment	Outcomes
Anitua, 2017[26]	19 (13 M, 6 F)	Five PRP + PRGF activator treatments injected into the scalp at months 0, 1, 2, 4, and 7	• Increase in mean hair density, diameter, and terminal/vellus hair ratio at 12 months compared with baseline • Increase in epidermal thickness, perifolliular neoangiogenesis, proliferative basal keratinocytes, and terminal/miniaturized hair ratio at 12 months compared with baseline
Borhan, 2015[27]	17 M	Four treatments of nonactivated PRP at weeks 0, 3, 6, and 12 injected over vertex	• Increased hair density in 11/14 evaluated by TrichoScan subjects at 4 months • Cosmetic assessment by Canfield stereotaxic system showed cosmetic improvement in only vertex of 2 cases according to 3 evaluators
Butt, 2018[28]	30 (20 M, 10 F)	Two PRP treatments injected into the scalp 4 weeks apart	Increase in mean hair density, increase in terminal/vellus hair ratio, and decrease in number of hairs during hair pull test at 6 months compared with baseline
Gkini, 2014[29]	22 (20 M, 2 F)	Three PRP treatments each 3 weeks apart, then 1 PRP treatment 6 months later into all subjects	Increase in hair density peaking at 3 months. Hair density decreasing at 6 months and 1 year but remained significantly higher than baseline
Ince, 2018[30]	80 M	• Group 1: nonactivated PRP • Group 2: activated PRP • Group 3: homologous PRP • PRP treatments injected at months 1, 2, and 6	• Increase hair density in all groups • Increase in hair density greatest in group 3 • Group 1 showed better results than group 2
James, 2016[31]	5	PRP treatments every 2–3 weeks over 3 months	Clinical improvement in hair counts, hair thickness, hair root strength, and overall alopecia at 6 months compared with baseline
Khatu, 2014[32]	11 M	Four PRP treatments every 2 weeks injected in a linear pattern 1 cm apart	• Increase in hair count after 4 treatments compared with baseline • 10/10 patients with positive pull test at baseline, 1/10 with positive pull test after 4 treatments
Marwah, 2014[33]	10 M	Six weekly PRP treatments	• 2/10 patients with clinical improvement based on global photography • All patients reported subjective improvement and satisfaction
Schiavone, 2014[34]	64	Two treatments of PRP 3 months apart	• Some clinical improvement seen in 64/64 patients and 62/64 patients by the 2 evaluators • Mean change in clinical rating was 3.2 and 3.9 by the 2 evaluators • Proportion of patients reaching clinically important difference was 40.6% and 54.7% by the 2 evaluators
Singhal, 2015[35]	10 (8 M, 2 F)	PRP treatments every 2–3 weeks over 3 months	• Clinical improvement in hair count, thickness, root strength, and overall alopecia at 6 months compared with baseline • Improvement in hair pull test with number of hair pulled out reduced by average of 65% at 6 months
Starace, 2018[36]	10 F	Four PRP treatments injected every 2 weeks	Increase in hair density and diameter, decrease in vellus hairs at 24 weeks compared to baseline

AGA, androgenetic alopecia; F, females; M, males; PRP, platelet-rich plasma.

> 10 years of AGA, suggesting possible characteristics that portend a better outcome.

Tawfik and Osman[21] conducted a randomized, half-head study in females with AGA. Unlike other studies, the authors chose to inject weekly for a total of 4 sessions. Follow up at 6 months revealed a significant increase in hair density and thickness as measured by a folliscope in PRP-treated scalp compared with the placebo half.

A few randomized controlled trials have failed to show any beneficial effects of PRP treatment for AGA. One of the first studies in female AGA randomly assigned women to receive either a single PRP treatment or saline injections into the scalp. At 26 weeks, no statistically significant difference in the hair count or hair mass was found.[22] It is important to note that the study design entailed only 1 injection of PRP, the preparation was diluted with PPP, and no activating substance was used, which may have contributed to the subpar results.[22] Mapar et al[23] recruited 17 men with severe AGA (stage IV-VI of the Norwood hair-loss classification) and injected 1 section of the scalp with PRP and another with saline in 2 sessions, 1 month apart. No difference was noted in the mean number of terminal

and vellus hairs. The authors contribute the inadequate response they obtained to the severity and longstanding duration of AGA in the study population.

In addition to the randomized controlled trials summarized above, numerous prospective cohort studies have been conducted, the majority of which support the efficacy of PRP for treating AGA. These studies and their respective findings are reviewed in Table 2.[26-36]

Various PRP formulations and protocols have been studied in an effort optimize efficacy. Injections of PRP supplemented with CD34 + cells, which are known to have angiogenic potential, resulted in a significant increase in mean hair number and thickness compared with baseline at 3 and 6 months, although no comparison was made with pure PRP preparations.[37] PRP has also been combined with dalteparin and protamine microparticles—carriers for controlled release of growth factors. Twenty-six patients were randomly assigned to receive PRP alone or PRP and dalteparin and protamine microparticles; although both groups showed clinical improvement, the latter exhibited more substantial changes.[38] Other formulations of PRP, including a gel-like formulation referred to as plasma-rich fibrin (PRF), as well as spray formulations, have been successfully utilized to treat AGA.[39,40] PRP has also been combined with other techniques, including suture embedding and microneedling, with positive clinical outcomes.[41,42]

Based on review of the published studies and our clinical experience, we suggest the optimal method for preparing PRP involves single-spin centrifugation both to produce pure PRP with a mean platelet enrichment of 3- to 6-fold compared with whole blood, and to minimize granulocytes. We recommend administration of PRP as subdermal depo bolus injections, as this is less painful and an overall more efficient injection technique. Subdermal depo bolus injections allow for diffusion of PRP, resulting in fewer injections. Injections should be spaced out over the thinning area, which is typically along the hairline, parting, vertex, and crown of the scalp. Treatment intervals should include 3 monthly sessions followed by a fourth session 6 months later (4 sessions over 12 months), then maintenance injections once every 12 to 18 months. Overall, we have achieved positive results when treating our male and female AGA patients with PRP injections in terms of regrowth, increased hair density, and improved quality of life (Figures 1 and 2).

Applications in Alopecia Areata

AA is a common immune-based destruction of hair follicles leading to well-circumscribed patches of sudden alopecia that can occur in various patterns. A number of therapies have been used with varying success including topical and intralesional steroids, systemic corticosteroids, minoxidil, anthralin, immunotherapy, and cyclosporine. PRP has recently been added to the repertoire of treatment for AA (Table 3).

The first double-blind, controlled trial utilizing PRP to treat AA randomly assigned 45 patients to receive PRP, intralesional triamcinolone acetonide, or placebo injections at monthly intervals for 3 months on half the scalp. Patients treated with PRP were found to have significantly increased hair regrowth when compared with both the intralesional triamcinolone and placebo groups. The PRP group also had significantly more patients who achieved complete remission at 12 months and significantly fewer patients with relapsed disease.[45]

A prospective study conducted in India included 20 patients with biopsy-proven patchy AA of at least 2 years duration; all subjects had failed to respond to various other treatments. These patients received 6 sessions of PRP at 4-week intervals. Of the 20 patients, only 1 patient showed minimum hair regrowth; this patient was also the only one whose condition was found to have relapsed at the 1-year follow-up.[44]

Another trial demonstrated the superiority of PRP over minoxidil for treating AA. Ninety patients were randomly assigned to receive either topical minoxidil 5% solution, PRP injections, or placebo.[44] Significant hair growth was seen in patchy alopecia in both the minoxidil and PRP groups compared with the placebo group. Patients treated with PRP had an earlier and better response when compared with the minoxidil group; PRP-treated patients had fully pigmented hair regrowth as well as decrease in both short vellus hair and yellow dots.[43]

STEM CELLS AND PEPTIDES

Introduction

Stem cells are defined by their ability to both self-renew and differentiate into other cellular subtypes. Multipotent stem cells reside in a number of adult tissues, including bone marrow and adipose tissue, and are integral to the regeneration of healthy tissue. In addition to tissue regeneration, stem cells release factors referred to as "secretomes" that have a variety of other effects such as wound healing and immunologic modulation.[46] Given these properties, stem cell therapy has emerged as an exciting solution in many fields, including hair restoration.

Mechanism of Action

The hair follicle contains a number of stem cell niches, including the bulge region, dermal papilla and the hair germ, that are essential to its regenerative capacity. Every hair follicle cycles between a growing phase (anagen), regression phase (catagen), and quiescent phase (telogen).[46]

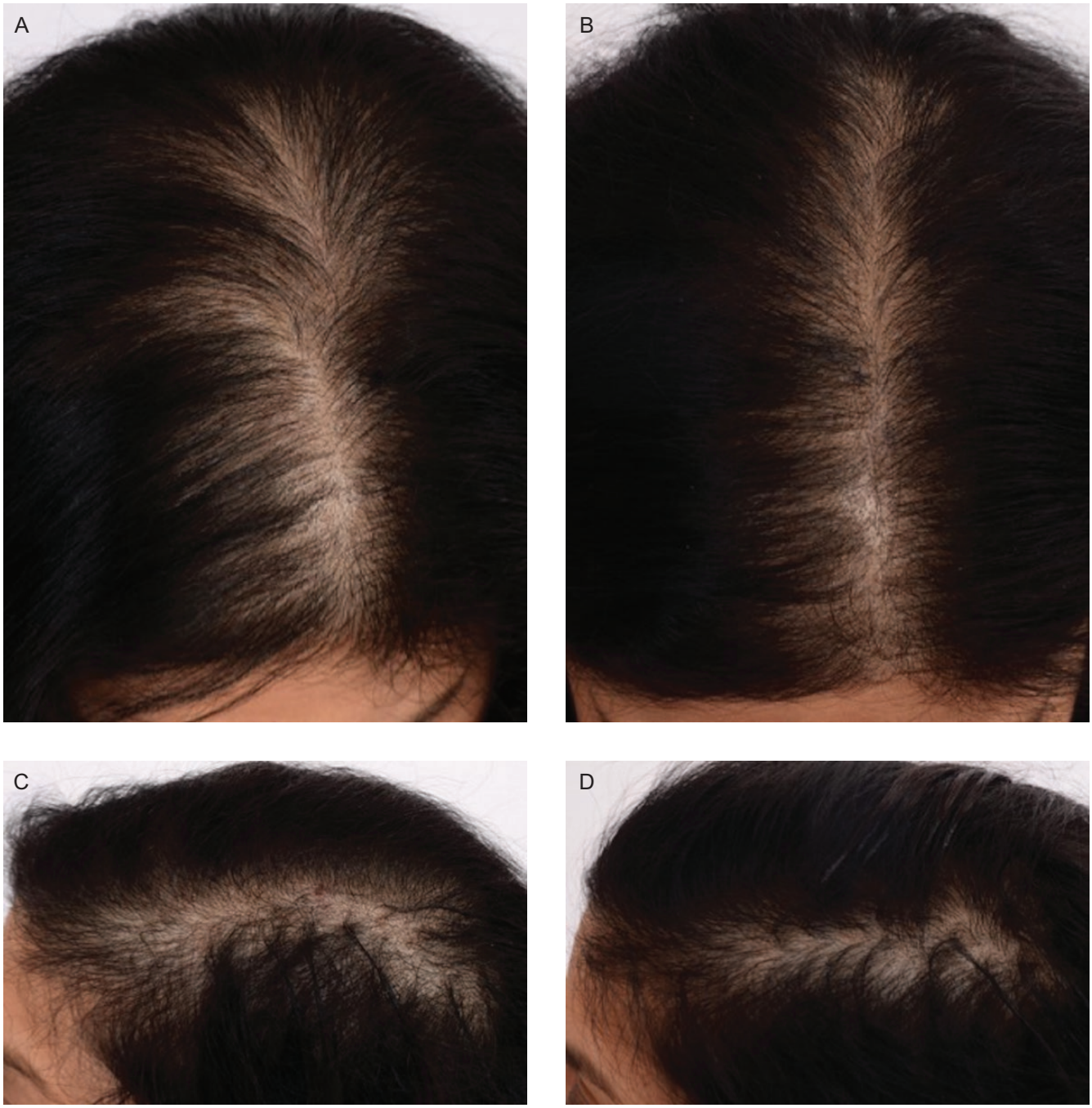

Figure 1. (A, C) A 42-year-old woman with androgenetic alopecia before PRP treatments. (B, D) Five months after 3 monthly PRP treatments. (B) Increased number of terminal hairs noted on the vertex and crown of the scalp, and (D) increased number of terminal hairs noted on the parietal scalp. PRP, platelet-rich plasma.

Follicular stem cells and their cross-talk play an essential role in producing the dramatic morphologic differences in the hair follicle observed at each phase. The cells in the hair germ are the first to begin proliferating and express the genes essential for activating other stem cells as the hair cycle transitions from the telogen to the anagen phase. Subsequently, the follicular bulge and dermal papilla stem cells begin to proliferate and differentiate to produce a new, robust hair shaft from the miniaturized telogen hair follicle.

The molecular mechanisms that govern these cells are mostly unknown, but a few molecular pathways have been identified that are essential to the regulation of stem cell activity and hair growth. During the telogen or

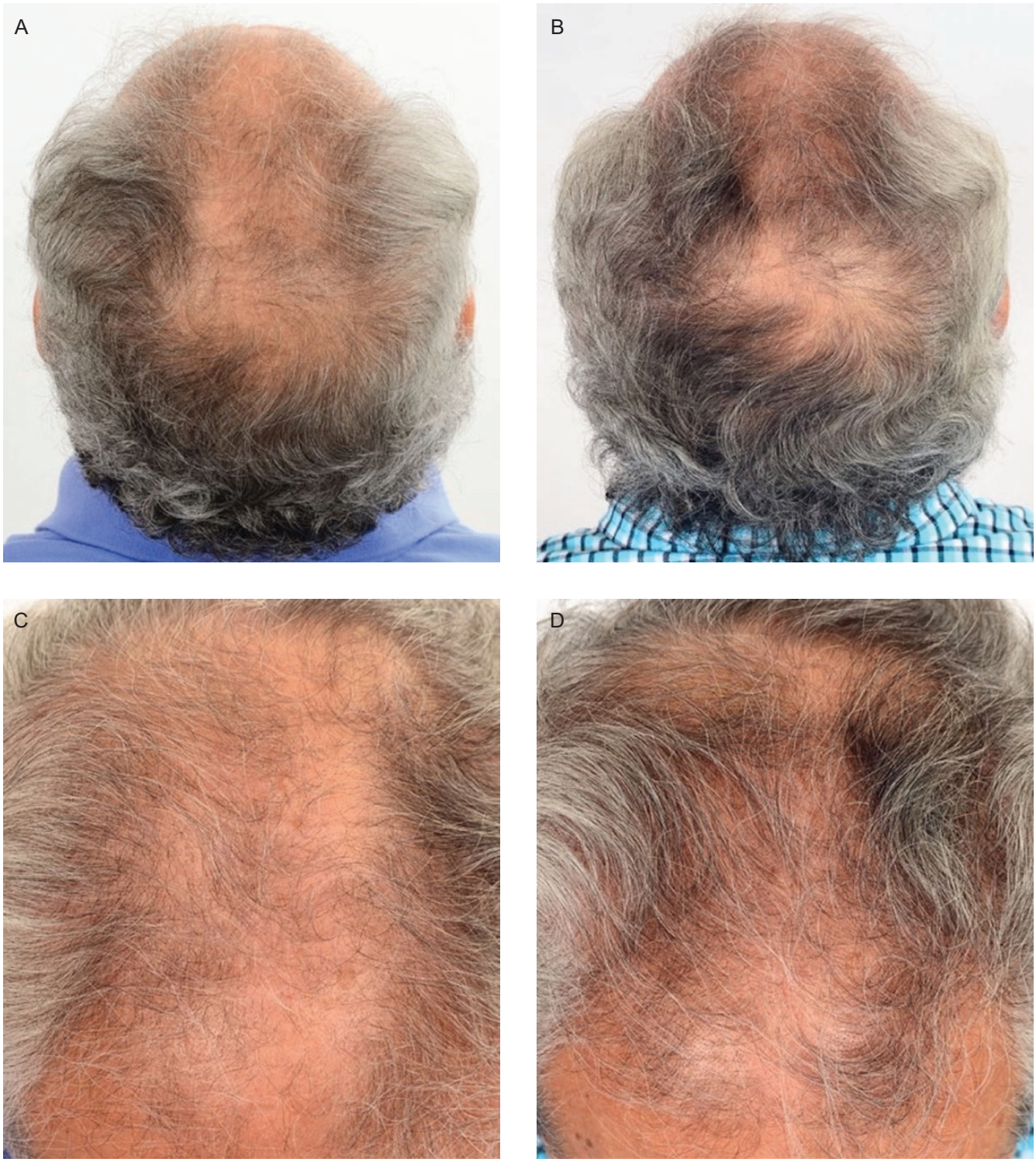

Figure 2. (A, C) A 69-year-old man with androgenetic alopecia before PRP treatments. (B, D) Four months after 3 monthly PRP treatments. (B) Increased number of terminal hairs noted on the vertex scalp and (D) increased number of terminal hairs noted on the crown of the scalp. PRP, platelet-rich plasma.

resting phase of the hair cycle, expression of bone morphogenetic protein (BMP), TGF-β, and FGF ligands, as well as Wnt inhibitors, occurs. A balance between these molecules is essential to maintain quiescence.[47] During the growing or anagen phase, Wnt signaling and β-catenin are upregulated to activate hair growth.[46-49] BMP ligands and

Table 3. Studies Evaluating the Effects of PRP in AA

Study, year	No. of patients	Study type	Treatment	Outcomes
El Taieb, 2016[43]	90 (39 M, 51 F)	RCT	• Group 1: topical minoxidil 5% twice daily • Group 2: 3 monthly PRP treatments • Group 3: placebo (topical panthenol cream twice daily)	• Significant hair growth in groups 1 and 2 compared with placebo • Earlier response, better response, and decrease in short vellus hair, yellow dots, and dystrophic hair in group 2 compared with groups 1 and 3
Singh, 2015[44]	20	Prospective study	Six monthly PRP treatments	Hair regrowth in all but 1 patient who experienced minimal hair regrowth and relapse
Trink, 2013[45]	45 (20 M, 25 F)	RCT	Randomized to receive 3 monthly treatments of intralesional injection of PRP, triamcinolone, or placebo to half of their scalp	• Increase in hair regrowth and decrease in hair dystrophy and burning/itching in PRP-treated scalp compared with the other 2 groups • Increase in Ki67 levels (markers of cell proliferation) in PRP-treated scalp compared with the other 2 groups

AA, alopecia areata; F, females; M, males; PRP, platelet-rich plasma; RCT, randomized controlled trial.

Notch signaling also have been recognized as essential for hair follicle differentiation.[47]

Applications in Hair Loss

Although application of stem cell therapy in hair restoration is relatively new, with varied preparations and applications, the results to date are promising.

Anderi et al[50] harvested autologous adipose-derived stromal vascular cells via lipoaspiration. These preparations were injected into the scalp of 20 patients with AA. In a retrospective analysis, the patients treated with adipose-derived stromal vascular cells showed a significant increase in hair diameter and density, as well as a decrease in the pull test at 3 and 6 months after treatment when compared with baseline.

Gentile et al[51] described a novel method to isolate human adult stem cells by the centrifugation of human hair follicles obtained via punch biopsy. These stem cells were injected into the scalps of 11 patients with AGA, resulting in an increase in hair density and hair count when compared with baseline and placebo.

Adipose-derived stem cell conditioned medium (ADS-CM), known to be rich in growth factors such as VEGF, HGF, PDGF, and insulin-like growth factor (ILGF), has also be utilized to treat hair loss.[52–54] Six injections of ADS-CM at 3- to 5-week intervals significantly increased hair numbers compared with baseline and placebo in patients with alopecia.[52,53] Significant increases in hair density and thickness were also noted after administration of ADS-CM by microneedle roller or mesotherapy gun weekly for 12 weeks in patients with AGA.[54]

Li et al[55] introduced a novel stem cell method, termed "stem cell educator therapy." In this technique, the patient's blood is circulated through a system that separates the mononuclear cells from whole blood, allows these separated cells to interact with human cord blood–derived multipotent stem cells, and returns the "educated" cells to the patient's circulation. Nine patients with severe AA received 1 treatment of this therapy. All but 1 patient experienced improved hair regrowth in varying degrees. Two patients (1 with alopecia totalis and 1 with patchy AA) experienced complete hair regrowth at 12 weeks without relapse after 2 years. These results were thought to be secondary to an upregulation of the Th2 cytokines and a restoration of balance between the Th1, Th2, and Th3 cytokine profiles.

Elmaadawi et al[56] randomly assigned 40 patients (20 with AGA and 20 with AA) to receive either autologous bone marrow–derived mononuclear cells or autologous follicular stem cell injections into the scalp. All groups were found to show significant improvement in hair loss with no statistically significant differences between the 2 preparations.

Interestingly, a combination of PRP and stem cell technology has shown promising results. Stevens et al[57] combined adipose-derived stromal cells from autologous adipose tissue with autologous PRP. The solution was injected once into a single area on the scalp of 10 men with AGA. A significant increase in hair density was observed at 6 and 12 weeks after injection in the treated side compared with baseline and the nontreated side. New terminal and vellus hairs were noted in existing, previously inactive, and possibly new follicles.

CONCLUSIONS

Based on the plethora of literature that has been published in recent years, PRP is a promising, minimally invasive, office-based procedure for hair-loss treatment. Safety issues and side effects appear to be minimal. Despite the promising literature, limitations to the studies exist. A standardized preparation and protocol, including optimal preparation, dose, number and interval of treatment sessions, and injection technique,

has yet to be determined. Most literature reports support monthly injections for at least 3 months, but the published studies employ a wide variety of methods. Similarly, the quantification of the results is highly varied in the literature. These limitations make it difficult to objectively compare and combine results to determine clinical efficacy. Further randomized placebo-controlled trials with larger sample sizes and longer follow-up periods are needed to establish the optimal PRP protocol, clinical efficacy, and long-term outcomes.

Disclosures

Dr Khetarpal is a consultant for Eclipse Aesthetics and has received research equipment and an honorarium, and is a speaker and trainer for Galderma and Allergan. Dr Semsarzadeh declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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