OPEN

PRS GLOBAL OPEN

ORIGINAL ARTICLE
Research

Autologous Stem Cell-derived Therapies for Androgenetic Alopecia: A Systematic Review of Randomized Control Trials on Efficacy, Safety, and Outcomes

Konstantinos Gasteratos, MD, MSc*
Konstantinos Kouzounis, BSc†
Jeremy Goverman, MD, FACS‡

Background: Androgenic alopecia (AGA), a prevalent and extensively studied condition characterized by hair loss, presents a significant global issue for both men and women. Stem cell therapy has emerged as a promising therapeutic approach for AGA due to its regenerative and immunomodulatory properties. The primary objective of this systematic review was to assess the current literature on the efficacy and safety of cellular and acellular stem cell–derived therapies in the management of AGA.

Methods: A computerized literature search was conducted in ClinicalTrials.gov, PubMed, and Cochrane Library in October 2023. The online screening process was performed by three independent reviewers with the Covidence tool. The protocol was reported using the Preferred Reporting Items for Systematic Review and Meta-Analyses, and it was registered at the International Prospective Register of Systematic Reviews of the National Institute for Health Research.

Results: The search yielded 53 articles from 2013 to 2023. Twelve randomized controlled trials were included. Stem cells and their derivatives were isolated from human adipose tissue, hair follicles, bone marrow, umbilical cord blood, and exfoliated deciduous teeth. These trials showed that stem cell–derived treatments can promote hair regeneration and density.

Conclusions: Both cellular and acellular stem cell–based therapies are safe and effective in improving hair regeneration and density in AGA patients. Although the outcomes may be temporary in some cases, regenerative treatments may become useful adjuncts in combination with traditional methods of hair transplantation. Future research should focus on protocol optimization to enhance long-term patient outcomes. *(Plast Reconstr Surg Glob Open 2024; 12:e5606; doi: 10.1097/GOX.0000000000005606; Published online 13 February 2024.)*

INTRODUCTION

Androgenic or androgenetic alopecia (AGA), often known as male pattern hair loss or female pattern hair loss (FPHL) is a common nonscarring alopecia that affects a large population globally. The person's physical and mental health are affected by the hair loss and reduction in hair volume.[1,2] Multifactorial AGA development involves a complex relationship between genetic predisposition and androgen hormone levels.[3] Currently, an annual global market revenue of US $4 billion is estimated for AGA treatments.[4–6]

Hair follicles (HFs) are complex miniorgans derived from the ectodermal (epithelial/epidermal)-mesodermal (mesenchymal) junction. The HF contains a matrix that derives from ectoderm and an underlying dermal papilla

*Formerly of Feinstein Institutes for Medical Research, Manhasset, N.Y.; †School of Medicine, St. George's University, Grenada, West Indies; and ‡Summer M. Redstone Burn Center, Department of Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, Mass.

Received for publication November 9, 2023; accepted January 5, 2024.

Gasteratos and Kouzounis contributed equally to this work.

DOI: 10.1097/GOX.0000000000005606

Disclosure statements are at the end of this article, following the correspondence information.

Related Digital Media are available in the full-text version of the article on www.PRSGlobalOpen.com.

that derives from mesoderm. The matrix is an area of rapid mitotic activity of undifferentiated cells, whereas the dermal papilla has androgen and growth factor receptors along with the vascular supply to the HF. Matrix cells are immunologically regulated.[7] The follicular unit is composed of terminal hairs, vellus hairs, sebaceous glands, arrector pili muscle (APM), and sympathetic nerve. APM and sympathetic neurons form a dual-component niche that regulates hair follicle mesenchymal stem cells (HF-MSCs or HFSCs) in the bulge region of HFs (Fig. 1). The preservation of CD34- and CD200-positive HFSCs within the occipital scalp[8,9] makes AGA reversible because they can differentiate into inter-follicular epidermis, HF structures, and sebaceous glands, thus allowing embryonic epithelial-mesenchymal driven organogenesis. Additionally, HFSCs secrete cytokines and exosomes.[10–15] In the progression of AGA, APM attachment to vellus hairs is lost, although attachment to terminal hairs remains preserved.

Because the efficacy of minoxidil and finasteride is not always assured across patients, as topical therapies have transient effects,[16] novel stem cell–derived therapies for AGA have emerged. These therapies are broadly divided into cellular and acellular ones. Cellular treatments consist of the transplantation of stem cells alone that modulate follicular cells, and hair cycles that replace dead cells. However, transplanted stem cells have several drawbacks: low survival rates and decreased regenerative properties in vivo, potential immune reactions, and invasiveness of harvesting procedures.

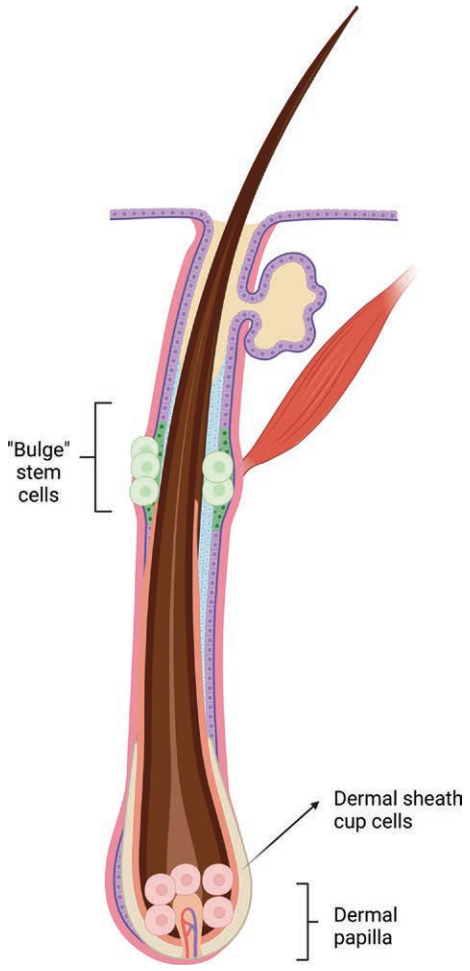

Fig. 1. The anatomy of a hair follicle depicts the presence of stem cells in several locations.

Takeaways

Question: What is the efficacy and safety of autologous cellular and acellular stem cell–derived therapies for androgenic alopecia?

Findings: A systematic review and analysis of randomized control trials retrieved 12 randomized control trials relevant to our inclusion criteria. Stem cells and their derivatives were isolated from human adipose tissue, hair follicles, bone marrow, umbilical cord blood, and exfoliated deciduous teeth. These trials showed that stem cell–derived treatments can promote hair regeneration and density.

Meaning: Although the outcomes may be temporary in some cases, cellular and acellular stem cell–based therapies for androgenic alopecia are a promising emerging solution.

Acellular interventions consist of cell-free conditioned media/extracts isolated from stem cells. By upregulating stem cell expression, there is an abundant release, in the nutrient conditioned media, of salutary factors that provide paracrine effects on neighboring cells by their angiogenic, hematopoietic, antiapoptotic, fibroblastic, and proinflammatory properties but also directly impact follicular growth by activation of stem cells and induction of the telogen-to-anagen transition.[15] These paracrine factors include growth factors (eg, vascular endothelial growth factor, VEGF, platelet-derived growth factor, PDGF, endothelial growth factor, EGF, and so on), cytokines (eg, interleukin-6, etc) and chemokines (eg, monocyte chemotactic protein-3, MCP-3, eotaxin, and so on).[17]

For example, vitamin D is synthesized in epidermal keratinocytes when exposed to UVB. As a hair-growth associator, vitamin D analog can upregulate the expression of transforming growth factor-beta 2 (TGF-β2), an index for hair-inductive capacity that promotes the differentiation of stem cell populations into dermal sheath cells (DSCs). VEGF increases hair growth and size by follicle vascularization.[18] Hair regrowth is regulated primarily by ERK activation and Wnt signaling.

The aim of this systematic review was to evaluate, analyze, and synthesize data from several randomized controlled trials (RCTs) to assess the efficacy and safety of stem cell–derived cellular and acellular therapeutic protocols for AGA and their outcomes.

MATERIALS AND METHODS

A comprehensive literature search was undertaken across three electronic databases (ClinicalTrials.gov, PubMed, Cochrane Library) to identify pertinent RCTs

Table 1. Search Strategy for Our Study

PubMed	Clinicaltrials.gov	Cochrane Central Register of Controlled Trials
((((“androgenic alopecia”[Title/Abstract]) OR (“androgenetic alopecia”[Title/Abstract])) OR (“male pattern hair loss”[Title/Abstract])) OR (“female pattern hair loss”[Title/Abstract])) NOT (finasteride[Title]))))	Condition: “androgenic alopecia”	MeSH descriptor: [Alopecia] explode all trees and with qualifier(s): [therapy - TH]
Filters: clinical trial, RCT, 10 years, English, Adults	Filters: Adults	—

Table 2. Inclusion and Exclusion Criteria of Our Systematic Review

Study Characteristics	Inclusion Criteria	Exclusion Criteria
Study design	RCTs to explore the efficacy of stem cell–based interventions in the treatment of AGA	Nonrandomized trials, observational studies, systematic reviews, or case reports have been identified as potential sources of data for analysis and investigation in the medical research field
Population	Patients with a history of AGA	Animals, patients without AGA
Intervention	Adipose-derived stem cells, stem cells derived from hair follicles, bone marrow, umbilical cord blood, and exfoliated deciduous teeth, and stem cell derivatives	PRP, nonstem-cell treatments, minoxidil, 5-a reductase, finasteride
Comparators	Control	None
Outcome	Hair regrowth, hair density, hair follicle diameter, and any potential adverse events.	Maintenance of hair follicles
Language	English	Non-English
Period	2013–2023	>10 years

AGA, androgenic alopecia; RCTs, randomized control trials.

on stem cell therapies for AGA in the past decade. Our search strategy is shown in Table 1. Keywords used were “androgenic/androgenetic alopecia,” and “male/ female pattern hair loss.”

Key outcomes were hair regrowth, hair counts, and hair density. The inclusion criteria were RCTs on stem cell–derived therapies for AGA published in English between 2013 and 2023. The exclusion criteria were low-evidence literature, experimental animal studies, other types of alopecia, minoxidil, and finasteride treatment alone (Table 2). The screening process and data extraction forms were facilitated with Covidence by the first two authors. These forms included study characteristics, participant demographics, intervention/treatment protocols, outcome measurements, and results. Our protocol was reported using the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA), and it was registered at the International Prospective Register of Systematic Reviews of the National Institute for Health Research (PROSPERO #CRD42023460620).

RESULTS

The presence of diverse effect sizes and heterogeneity among studies highlights the inherent variability of stem cell interventions, treatment protocols, and participant populations. Therefore, a systematic review was performed without a meta-analysis. We identified 12 RCTs between 2013 and 2023 that met our inclusion criteria. Currently, there are no published RCTs on exosomes for AGA. The selection process is illustrated in the PRISMA flowchart (Fig. 2). These studies pertain to five cellular and eight acellular types of stem cell–derived therapies which will be discussed further below. A total of 514 participants with AGA were included in these studies. The detailed characteristics of these RCTs with their therapeutic interventions, strengths, and limitations are shown in Supplemental Digital Contents 1 and 2. (**See table 1, Supplemental Digital Content 1,** which displays the RCTs on cellular and acellular treatments for AGA with patient demographics and results. **http://links.lww.com/PRSGO/D67**.) (**See table 2, Supplemental Digital Content 2,** which displays the RCTs on cellular and acellular treatments for AGA with conclusions and study innovations-limitations. **http://links.lww.com/PRSGO/D68**.)

DISCUSSION

A visual summary of the therapeutic interventions to be discussed is shown in Figure 3. The following categorization was primarily based on the type of tissue harvested, and secondarily on the cellular or acellular intervention.

I. Hair Follicle Interventions

a. Acellular

An RCT by Gan et al [19] examined the efficacy of autologous HF-MSC suspension therapy in 50 Chinese AGA patients (ages 25–45 years). Healthy HFs were extracted from the occipital area and were processed to obtain HF-MSC suspensions, which were then injected in a 1 cm^2 area of the receding hairline (intervention group versus normal saline, placebo). The duration of follow-up was 9 months. An increased proportion of terminal hair and hair shaft diameter was observed in the experimental group at 1 month; the effect lasted 3 months, as cell therapy may be limited by their survival in vivo. Gan et al found that 60 μm was a significant index for evaluating the progress of AGA, as the hair thickening effect of advanced miniaturized HFs with hair shaft diameter less than 60 μm was more notable than that above 60 μm.

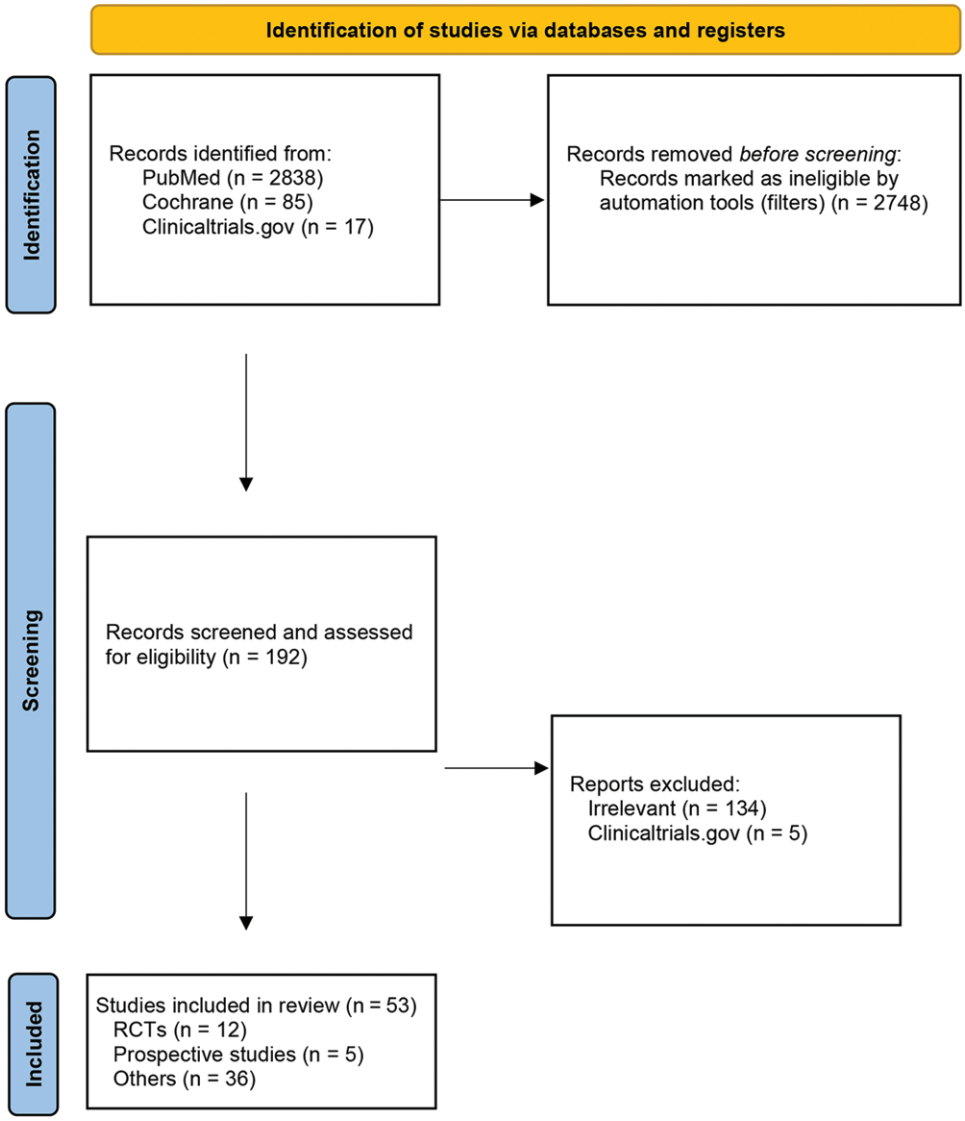

Fig. 2. PRISMA flow chart of studies.

b. Cellular

In their RCT, Gentile et al[20] used an innovative protocol for obtaining autologous HF-MSC micrografts containing human intra- and extradermal adipose-derived hair follicle stem cells (HD-AFSCs). HD-AFSCs are considered the cellular population containing HF-MSCs and hair follicle epithelial stem cells (HF-ESCs). Scalp injections were performed with a mesotherapy gun in 17 men and 10 women with AGA. After 58 weeks, patients displayed an increase in hair count and density of 18.0 hairs per 0.65 cm^2 and 23.3 hairs per cm^2, respectively, whereas the control area (treated with normal saline) displayed a mean decrease of 1.1 hairs per 0.65 cm^2 and 0.7 hairs per cm^2 ($P < 0.0001$). After 26 months, six patients revealed dynamic hair loss. No side effects were reported.

Tsuboi et al[21] examined the efficacy of autologous DPCs harvested from the occipital region in 65 patients with male pattern hair loss (n = 50) and FPHL (n = 15), ages 33–64 years. Participants received 1 mL injections of three different DSC suspension concentrations (7.5×10^6, 1.5×10^6, or 3.0×10^5 cells) or placebo (without cells). After 6- and 9-months post-DSC injections at the targeted area, hair density and strand width increased significantly. This effect was stronger at a lower dosage (3.0×10^5 DSCs/cm^2 of the scalp) than with a placebo. Injection sites showed erythema, purpura, and minor hemorrhages. Importantly, the positive effect was temporary for 9 months. This research highlights the significance of stem cell therapy dosage in the context of AGA. The injection of a high dose of DSCs into a localized area of the scalp may induce micro-inflammation due to tissue damage, cellular death, and debris. This inflammation could potentially affect the effectiveness of the treatment because of immune cell migration and toxicity in the local environment for the remaining viable DSCs.[19,21]

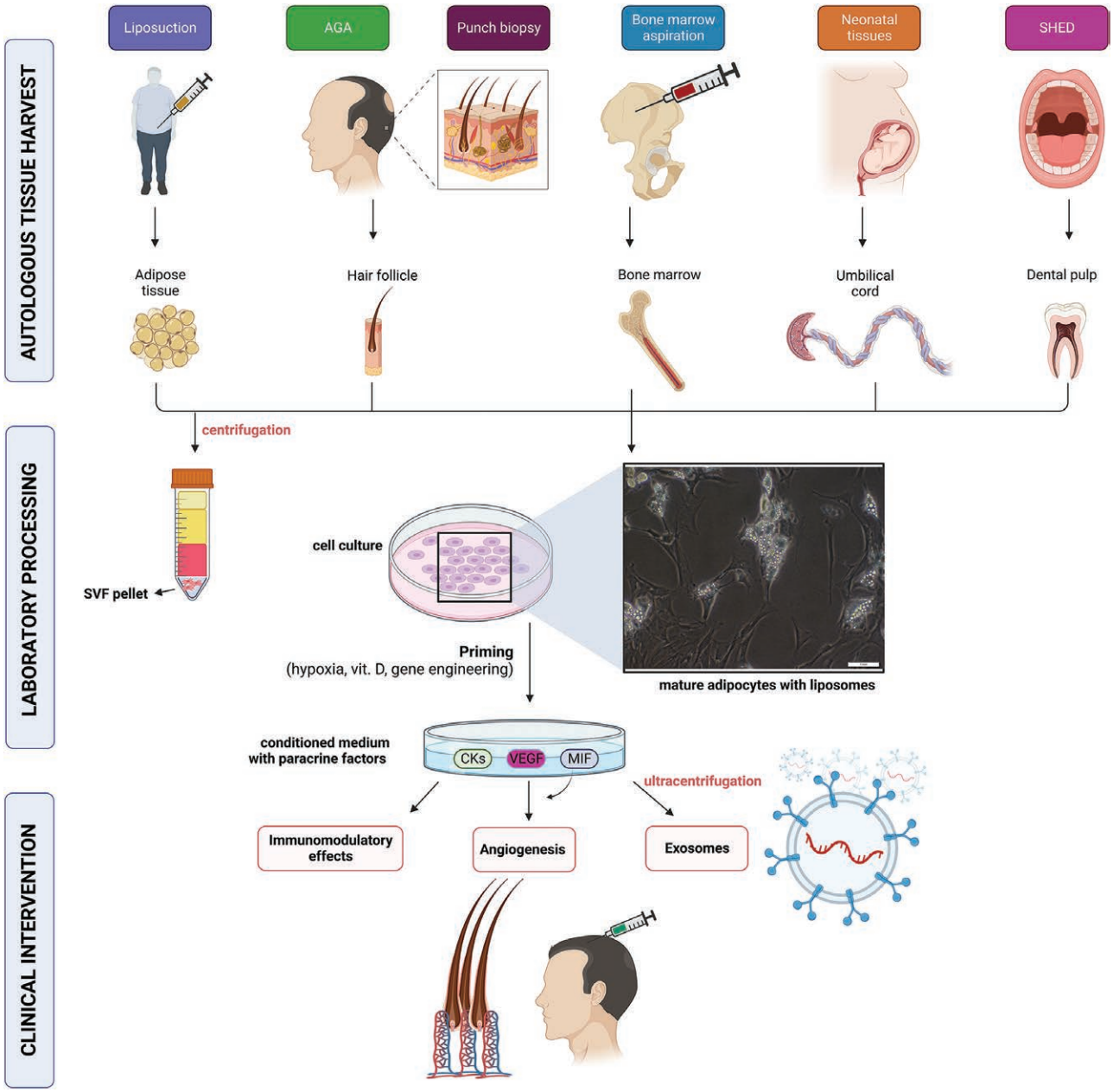

Fig. 3. Stem cell–based therapies for AGA from bench to bedside. Effective strategies for upregulating the therapeutic effects of stem cells: environmental stimulation (eg, hypoxia, ultraviolet B radiation), biostimulation (eg, vitamin D), and gene engineering (eg, trichogenic factors).

II. Adipose Tissue

a. Acellular Interventions (ADSC Secretome)

Tak et al[18] undertook a double-blinded RCT with 38 patients (ages 18–59). The intervention group (n = 19) self-administered topical solution of 2 mL of ADSC constituent extract (ADSC-CE) twice daily for 16 weeks, and the control group (n = 19) a placebo. A phototrichogram analysis showed an increase in hair count in the ADSC-CE group compared with the placebo group (17.58 ± 4.13 versus 13.95 ± 4.01 counts/cm^2, $P = 0.009$). No severe adverse effects were reported.

In an RCT, Lee et al[22] examined a cohort of 30 men and women with AGA (ages 20–61). To increase the trans-epidermal delivery and absorbance of human ADSC-CM through the scalp, a single session of nonablative fractional laser treatment was performed before the weekly topical microneedling applications of ADSC-CM or normal saline (placebo) for 12 weeks. The ADSC-CM group had significantly higher hair densities versus the placebo group (102.1 ± 4.09/cm^2 versus 89.3 ± 3.79/cm^2, $P < 0.05$, respectively), as well as global improvement scores. No adverse effects were noted.

In a 2023 RCT by Legiawati et al on 37 AGA men, phototrichogram and clinical photography showed that the combination of 2 mL ADSC-CM intradermal scalp injections followed by topical minoxidil 5% twice daily versus

normal saline injections (placebo) and minoxidil led to significant increases in hair count, density, and mean thickness after 6 weeks, minimum side effects, and subjects' satisfaction with results.[23]

Fukuoka et al[24] performed a study on 21 patients (16 AGA and five FHPL; age range: 27–69 years). Intradermal scalp injection of an ADSC-CM formulation (also known as advanced adipose-derived stem cell protein extract, AAPE) delivered 3–4 mL of AAPE. AAPE is cultured under hypoxic conditions to enhance cytokine secretion from ADSCs, and it is usually co-administered with vitamins, coenzyme Q10, and amino acids as nappage mesotherapy to boost antioxidant activity and hair growth. A monthly injection is repeated six to eight times. A substantial increase in hairs was observed 3 months after the first therapy (141.3 ± 31.4 versus 109.8 ± 43.5, respectively; $P < 0.01$). In a retrospective study (n = 27), Shin et al[25] used the same methodology of hypoxia-induced priming of ADSCs, except the subjects used a microneedle roller. Hair density and thickness increased and none of the patients reported severe adverse reactions after 12 weeks of treatment.

In a clinical trial by Narita et al,[26] 40 patients (21 men with AGA, 19 women with FPHL; age range, 23–74 years) were treated by intradermal injection of ADSC-CM every month for 6 months. Hair density, anagen hair rate, and ultrasonographic parameters (dermal thickness and echogenicity) were significantly increased.

b. Cellular Interventions

Kuka et al[27] conducted a clinical trial in a cohort of 17 women and 54 men, 24–73 years of age; 16 were treated with intradermal and subcutaneous scalp injections of Puregraft fat and 1.0×10^6 autologous adipose-derived regenerative cells (ADRCs) per cm^2 scalp, 22 with Puregraft fat and 0.5×10^6 ADRCs per cm^2 scalp, 24 with Puregraft fat alone, and nine with saline (control). They found statistically significant increases in terminal hair count for the low-dose ADRC group in the Norwood Hamilton 3 subgroup at week 24. Despite positive results, these were observed only in men with early hair loss, which likely requires additional treatments and/or complementary therapies (PRP, microneedling, LASER, etc.). No unanticipated adverse events were noted during the study. Puregraft fat and ADRCs were obtained from the patient's fat tissue with liposuction and additional processing. ADRCs maintain the ability to differentiate into mesenchymal lineage cells but also secrete various growth factors that seem to play a role in neovascularization, which is important in treating various hair loss conditions. The addition of adipose tissue in the scalp thickens the subcutaneous layer that is typically associated with thinning in AGA. Cell enrichment of adipose tissue with ADRCs has been shown to prolong graft retention.

Kim et al[28] used autologous adipose-derived stromal vascular fraction (SVF), which includes stem, vascular, and immune cells to restore hair growth by activating surrounding tissues with cytokines. In their study, nine patients with AGA (ages 43–64) received a single SVF scalp injection of $7–9 \times 10^6$ cells. At 6 months, a 48.11% increase in hair density was observed in the treated site compared with 35.48% in the nontreated site. Most of the subjects were satisfied with the result after treatment.

c. Combination of Cellular and Acellular Interventions

Papakonstantinou et al[29] found that autologous platelet-rich plasma (PRP) injections significantly increased the number of HFs, thickness, and density compared with placebo interventions. In their RCT (n = 22), Butt et al[30] found that the combined SVF-PRP group had a 51.64% increase in hair density after treatment ($P = 0.006$). The percentage reduction in the pull test was more significant in the SVF-PRP group (80.78 ± 5.84) versus the PRP group (34.01 ± 22.44). The physician and patient assessment scores also indicated a significant improvement in the SVF-PRP group. It has been postulated that SVF cells may promote hair regeneration by increasing the hair-inducing ability of DPCs.[31,32] In AGA patients, the basic concept of using SVF-enriched PRP is to replenish the HFSC repository in the bulge region by homing, and also to stimulate the growth cycle of stem cells by paracrine effects.[33]

III. Autologous Bone Marrow–derived Mononuclear Cells

Elmaadawi et al[34] studied 20 resistant cases of AGA patients (eight men, 12 women, ages 10–50 years) who were tested for the safety and efficacy of autologous bone marrow–derived mononuclear cells (BMMCs; mixture of progenitor cells, hematopoietic cells, a variety of inflammatory cell types, and MSCs; harvested under general anesthesia as bone marrow aspirate from the superior iliac crest) versus autologous follicular stem cells. All patients were resistant to conventional therapies and did not receive any treatment for alopecia for 6 months before enrollment. The cohort had two 10-patient groups. The two groups received a single session of intradermal injections of BMMCs or HFSCs. Six months postinjection therapy, immunostaining, and digital dermatoscopy showed a significant increase in hair strand width and HFs. Results showed a mean improvement percentage of 52 ± 28 for BMMCs and 42 ± 27 for follicular stem cells in AGA patients ($P = 0.426$).

Granulocyte colony-stimulating factor treatment before bone marrow aspiration caused fatigue and chills in certain patients. Bone pain and hematomas occurred in 80% of research subjects. The administration of analgesics effectively mitigated all symptoms. FSC therapy showed only scalp dermatitis in 25% of patients, which was resolved by emollients. Of note, this study also examined the treatment of alopecia areata in a different cohort. This study highlights the role of hematopoietic stem cells in hair regeneration; immunomodulatory functions, homing to inflammation sites, antiinflammatory effects, multipotency, and secretion of VEGF, which controls hair growth and follicle size through angiogenesis.

IV. Human Umbilical Cord Blood-derived Mesenchymal Stem Cells: Acellular Interventions

An RCT by Park (NCT03676400)[35] examined a cosmetic hair serum (NGF-574H) after repeated topical

Table 3. Advantages and Disadvantages of Each Technique for Harvesting Stem Cells from Body Tissues

Technique	Advantages	Disadvantages
Skin punch biopsy	Minimally invasive Minimal pain under LA Minimal downtime	Requires accuracy and expertise Laboratory facilities for processing by experienced staff Expensive procedures Micrografts may not take Donor sites may create visible scarring
Liposuction	Minimally invasive (for purposes of hair regeneration) Minimal pain under local anesthetic infiltration/sedation Secondary gain of liposculpture/defined contour 100–1000 times more stem cells than bone marrow Less need for long-term in vitro culture→ less risk of chromosomal abnormalities/malignant transformation High affinity for 3D scaffolds ADSCs high proliferative capacity and differentiation in vitro CM/CE more ethical treatment than stem cells	Requires experienced surgeon Laboratory facilities for processing by experienced staff Costly Moderate downtime SVF obtained from adipose tissue can be prepared within 2 hours to be used clinically
Bone marrow aspirate	Benefits of BMMCs: Large amounts of stem cells Homing to site of injury/inflammation Lack of immunogenicity Multipotency Regenerative/ antiapoptotic potential	Invasive Expensive Requires accuracy and expertise Laboratory facilities for processing and banking by experienced staff Potential complications (pain, ecchymoses, hematoma)
Umbilical cord blood harvest	Noninvasive (after delivery) No discomfort	Ethical dilemmas Invasive (during pregnancy) Limited storage of umbilical cord blood as compared with bone marrow Limited cell counts in cord blood High cost for storage Risk of complications (infection, radiation to fetus) during collection process
Exfoliated deciduous teeth harvest	Noninvasive Minimal side effects Low risk of ethical implications	Lack of long-term outcomes Difficulty in obtaining enough stem cells

applications to the scalp and hairs (twice daily) for 24 weeks in 84 Asians with AGA, 18–60 years old. NGF-574H is obtained by the collection of paracrine factors secreted by human umbilical cord blood–derived mesenchymal stem cells (hUCB-MSCs) that were exposed in vitro to an artificially designed environment mimicking the alopecia state. It is currently being used in Korea as a hair regeneration product with hUCB-MSC media as one of its inactive ingredients.[36]

Additionally, an RCT (n = 30; ages 20–60 years) by Oh et al[37] showed that macrophage migration inhibitory factor in the 5% (v/v) primed conditioned medium (with TGF-β2) secreted by hUCB-MSCs stimulated hair growth via VEGF-related β-catenin and phosphorylated-glycogen synthase kinase (p-GSK) signaling pathway in DPCs. At 16 weeks, the mean hair thickness in the test group was increased by 28.19% and, at 16 weeks, the mean rate of hair growth by 19.54% ($P < 0.001$). No severe adverse effects were noted. This is an important study that elucidates the molecular mechanisms of hair regeneration.

V. Stem Cells from Human Exfoliated Deciduous Teeth: Acellular Intervention

Kamishima et al[38] found that after 9 months, six human exfoliated deciduous (SHED-CM) scalp injections at one-month intervals were effective for 75% of AGA subjects (n = 33 men; mean age 52.8 years). Adverse effects including pain and small hemorrhages were transient and mild. A scoring system of three trichoscopic factors (maximum hair diameter, vellus hair rate, and multihair follicular unit rate) can be a possible predictor of SHED-CM efficacy.

Strengths and Limitations of Our Study

Despite the heterogeneity of the studies (dosage, type of stem cell therapy, method of harvest, follow-up periods, etc.) that may skew the results, our standardized methodological approach to collecting and analyzing data ensured objective assessment and reporting of advantages and disadvantages of each technique for harvesting stem cells from body tissues (Table 3). Also, individual characteristics, such as age, sex, and co-morbidities, as well as dosage and route of administration can significantly affect the efficacy of the intervention.

Future Perspectives and Emerging Cellular and Acellular Therapies

Although the results are temporary in the RCTs on HF-MSCs and DSCs, the possibility of repeat injections at predetermined time intervals should be considered in further research. Investigating how specific genetic markers and biomarkers relate to treatment responses can lead to more effective personalized therapies. Studies by Lee at el and Legiawati had particularly short follow-up periods; hence, prospective studies should focus on multicenter RCTs with longer surveillance duration to capture long-term outcomes on safety and efficacy.

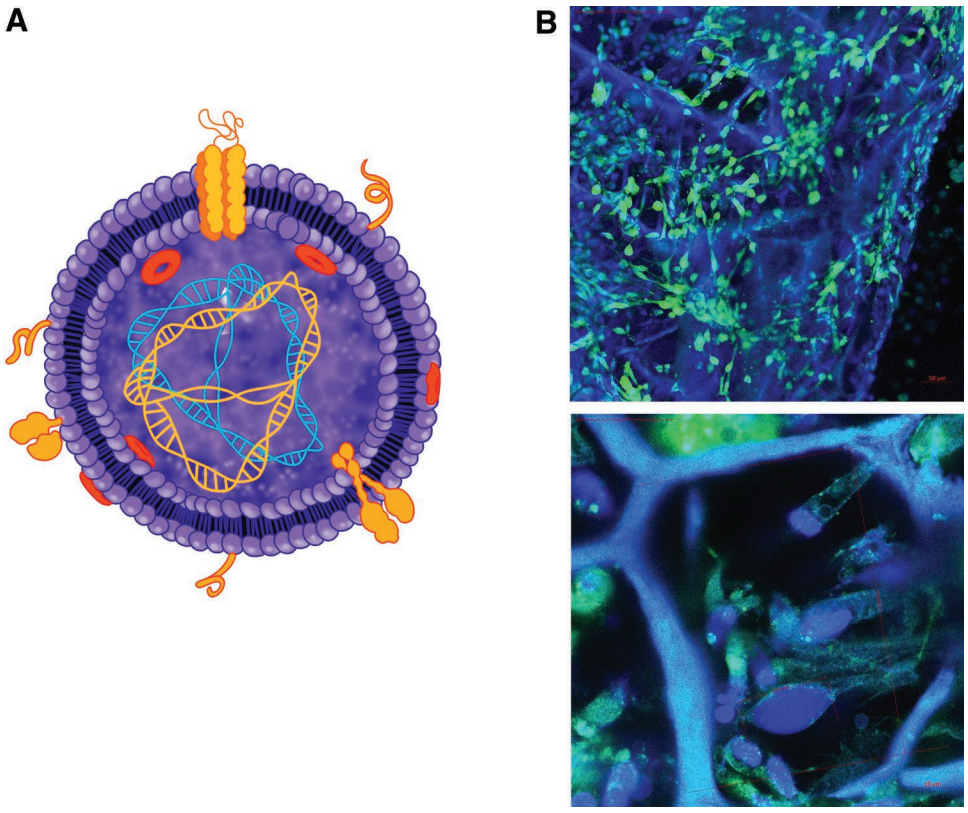

Fig. 4. Emerging regenerative medicine applications for AGA treatment. A, The external and internal structure of exosomes. During the biogenesis of exosomes, they are selectively filled with cellular bioactive cargo molecules. Their role in intracellular communication, physiological and pathological processes through their regenerative, antiinflammatory, and immunomodulatory functions is under investigation. B, Confocal fluorescence microscopic photographs (50 and 10 μm) of GFP-labeled (green color) Hoechst-stained (blue nuclei) ADSCs attached in a 3D biological scaffold (blue color) (image courtesy of primary author).

Bioengineering reprogramming of somatic cells (blood, skin cells) from a person with AGA leads to autologous induced pluripotent stem cells,[39] which differentiate into a variety of cell types (melanocytes, DPCs, and epithelial cells) that constitute a functioning HF. Induced pluripotent stem cells provide a virtually endless pool of folliculogenic cells for de novo creation of HFs.

Recent studies on ADSC-exosomes (Fig. 4A)[40] and human bone marrow MSC-derived extracellular vesicle isolate[41] showed promising results to treat AGA. It has been found that human ADSCs within the dermal white adipose tissue have stimulatory effects on DPCs and promote HF cycling via extracellular vesicles and complex signaling pathways.[15,42–47] Finally, HF organoids[48] and 3D scaffolds (Fig. 4B) are emerging solutions with clinical applications in virtually all aspects of regenerative plastic surgery.[49–53]

CONCLUSIONS

Both cellular and acellular stem cell–based therapies are safe and effective in improving hair regeneration and density in AGA patients. Although the outcomes may be temporary in some cases, regenerative treatments may become useful adjuncts in combination with traditional methods of hair transplantation. Future research should focus on protocol optimization to enhance long-term patient outcomes.

Jeremy Goverman, MD, FACS
Summer M. Redstone Burn Center
Department of Surgery
Massachusetts General Hospital
55 Fruit Street
Gray Bigelow Building, Suite 1303
Boston, MA 02114
E-mail: jgoverman@mgh.harvard.edu
Twitter: @jgoverman1

DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

REFERENCES

1. Alfonso M, Richter-Appelt H, Tosti A, et al. The psychosocial impact of hair loss among men: a multinational European study. *Curr Med Res Opin.* 2005;21:1829–1836.
2. Cash TF. The psychosocial consequences of androgenetic alopecia: a review of the research literature. *Br J Dermatol.* 1999;141:398–405.

3. Ellis JA, Sinclair R, Harrap SB. Androgenetic alopecia: pathogenesis and potential for therapy. *Expert Rev Mol Med.* 2002;4:1–11.
4. Norwood OT. Male pattern baldness: classification and incidence. *South Med J.* 1975;68:1359–1365.
5. Gatherwright J, Liu MT, Amirlak B, et al. The contribution of endogenous and exogenous factors to male alopecia: a study of identical twins. *Plast Reconstr Surg.* 2013;131:794e–801e.
6. Talavera-Adame D, Newman D, Newman N. Conventional and novel stem cell based therapies for androgenic alopecia. *Stem Cells Cloning.* 2017;10:11–19.
7. Rahmani W, Sinha S, Biernaskie J. Immune modulation of hair follicle regeneration. *NPJ Regen Med.* 2020;5:9.
8. Garza LA, Yang C-C, Zhao T, et al. Bald scalp in men with androgenetic alopecia retains hair follicle stem cells but lacks CD200-rich and CD34-positive hair follicle progenitor cells. *J Clin Invest.* 2011;121:613–622.
9. Waters JM, Richardson GD, Jahoda CAB. Hair follicle stem cells. *Semin Cell Dev Biol.* 2007;18:245–254.
10. Tumbar T, Guasch G, Greco V, et al. Defining the epithelial stem cell niche in skin. *Science.* 2004;303:359–363.
11. Cotsarelis G, Sun TT, Lavker RM. Label-retaining cells reside in the bulge area of pilosebaceous unit: implications for follicular stem cells, hair cycle, and skin carcinogenesis. *Cell.* 1990;61:1329–1337.
12. Gentile P, Garcovich S. Advances in regenerative stem cell therapy in androgenic alopecia and hair loss: WNT pathway, growth-factor, and mesenchymal stem cell signaling impact analysis on cell growth and hair follicle development. *Cells* 2019;8:466.
13. Gentile P, Alves R, Cole JP, et al. AIRMESS—Academy of International Regenerative Medicine & Surgery Societies: recommendations in the use of platelet-rich plasma (PRP), autologous stem cell-based therapy (ASC-BT) in androgenetic alopecia and wound healing. *Expert Opin Biol Ther.* 2021;21:1443–1449.
14. Fuchs E. The tortoise and the hair: slow-cycling cells in the stem cell race. *Cell.* 2009;137:811–819.
15. Yuan A-R, Bian Q, Gao J-Q. Current advances in stem cell-based therapies for hair regeneration. *Eur J Pharmacol.* 2020;881:173197.
16. Gupta AK, Charrette A. The efficacy and safety of 5α-reductase inhibitors in androgenetic alopecia: a network meta-analysis and benefit-risk assessment of finasteride and dutasteride. *J Dermatolog Treat.* 2014;25:156–161.
17. Andjelkov K, Eremin II, Korac A. Different levels of EGF, VEGF, IL-6, MCP-1, MCP-3, IP-10, Eotaxin and MIP-1α in the adipose-derived stem cell secretome in androgenetic alopecia. *Exp Dermatol.* 2022;31:936–942.
18. Tak YJ, Lee SY, Cho AR, et al. A randomized, double-blind, vehicle-controlled clinical study of hair regeneration using adipose-derived stem cell constituent extract in androgenetic alopecia. *Stem Cells Transl. Med.* 2020;9:839–849.
19. Gan Y, Du L, Wang H, et al. A clinical trial of treating androgenic alopecia with mesenchymal stem cell suspension derived from autologous hair follicle. *Plast Reconstr Surg.* 2023. [Online ahead of print.]
20. Gentile P, Scioli MG, Cervelli V, et al. Autologous micrografts from scalp tissue: trichoscopic and long-term clinical evaluation in male and female androgenetic alopecia. *Biomed Res Int.* 2020;2020:7397162.
21. Tsuboi R, Niiyama S, Irisawa R, et al. Autologous cell-based therapy for male and female pattern hair loss using dermal sheath cup cells: a randomized placebo-controlled double-blinded dose-finding clinical study. *J Am Acad Dermatol.* 2020;83:109–116.
22. Lee YI, Kim J, Kim J, et al. The effect of conditioned media from human adipocyte-derived mesenchymal stem cells on androgenetic alopecia after nonablative fractional laser treatment. *Dermatol Surg.* 2020;46:1698–1704.
23. Legiawati L, Suseno LS, Sitohang IBS, et al. Combination of adipose-derived stem cell conditioned media and minoxidil for hair regrowth in male androgenetic alopecia: a randomized, double-blind clinical trial. *Stem Cell Res Ther.* 2023;14:210.
24. Fukuoka H, Narita K, Suga H. Hair regeneration therapy: application of adipose-derived stem cells. *Curr Stem Cell Res Ther.* 2017;12:531–534.
25. Shin H, Ryu HH, Kwon O, et al. Clinical use of conditioned media of adipose tissue-derived stem cells in female pattern hair loss: a retrospective case series study. *Int J Dermatol.* 2015;54:730–735.
26. Narita K, Fukuoka H, Sekiyama T, et al. Sequential scalp assessment in hair regeneration therapy using an adipose-derived stem cell-conditioned medium. *Dermatol Surg.* 2020;46:819–825.
27. Kuka G, Epstein J, Aronowitz J, et al. Cell enriched autologous fat grafts to follicular niche improves hair regrowth in early androgenetic alopecia. *Aesthet. Surg. J.* 2020;40:NP328–NP339.
28. Kim SJ, Kim MJ, Lee YJ, et al. Innovative method of alopecia treatment by autologous adipose-derived SVF. *Stem Cell Res Ther.* 2021;12:486.
29. Papakonstantinou M, Siotos C, Gasteratos KC, et al. Autologous platelet-rich plasma treatment for androgenic alopecia: a systematic review and meta-analysis of clinical trials on patient safety, efficacy and outcomes. *Plast Reconstr Surg.* 2022;151:739e–747e.
30. Butt G, Hussain I, Ahmad FJ, et al. Stromal vascular fraction-enriched platelet-rich plasma therapy reverses the effects of androgenetic alopecia. *J Cosmet Dermatol.* 2020;19:1078–1085.
31. Katz A. Point-of-care adipose-derived cells for hair growth. Gainesville, Fla: University of Florida. Available at https://classic.clinicaltrials.gov/ct2/show/NCT02729415?term=stem&cond=Androgenetic+Alopecia&draw=2&rank=10. Accessed October 1, 2023.
32. Mantovani GP, Marra C, De Maria F, et al. Adipose-derived stromal vascular fraction (SVF) for the treatment of androgenic alopecia (AGA): a systematic review. *Acta Biomed.* 2023;94:e2023236.
33. Zuk PA, Zhu M, Ashjian P, et al. Human adipose tissue is a source of multipotent stem cells. *Mol Biol Cell.* 2002;13:4279–4295.
34. Elmaadawi IH, Mohamed BM, Ibrahim ZAS, et al. Stem cell therapy as a novel therapeutic intervention for resistant cases of alopecia areata and androgenetic alopecia. *J Dermatolog Treat.* 2018;29:431–440.
35. Hair growth efficacy and safety of NGF-574H in adult with androgenic alopecia. Available at https://classic.clinicaltrials.gov/ct2/show/NCT03676400?cond=NCT03676400&draw=2&rank=1. Accessed October 1, 2023.
36. Nih F. 574H CELL CARE—zinc pyrithione, panthenol, niacinamide, biotin shampoo. *FDA.report.* Available at https://fda.report/DailyMed/6b1dab05-16b0-4947-875d-48f8b4a3b1d9. Accessed October 1, 2023.
37. Oh HA, Kwak J, Kim BJ, et al. Migration inhibitory factor in conditioned medium from human umbilical cord blood-derived mesenchymal stromal cells stimulates hair growth. *Cells.* 2020;9:1344.
38. Kamishima T, Hirabe C, Ohnishi T, et al. Trichoscopic evaluation of dental pulp stem cell conditioned media for androgenic alopecia. *J Cosmet Dermatol.* 2023;22:3107–3117.
39. Pinto A, Terskikh AV. The rise of induced pluripotent stem cell approach to hair restoration. *Plast Reconstr Surg.* 2021;148:39S–46S.
40. Park B-S, Choi H-I, Huh G, et al. Effects of exosome from adipose-derived stem cell on hair loss: a retrospective analysis of 39 patients. *J Cosmet Dermatol.* 2022;21:2282–2284.
41. Sasaki GH. Clinical use of extracellular vesicles in the management of male and female pattern hair loss: a preliminary retrospective institutional review board safety and efficacy study. *Aesthet Surg J Open Forum.* 2022;4:ojac045.

42. Kruglikov IL, Zhang Z, Scherer PE. The role of immature and mature adipocytes in hair cycling. *Trends Endocrinol Metab.* 2019;30:93–105.
43. Owczarczyk-Saczonek A, Wociór A, Placek W, et al. The use of adipose-derived stem cells in selected skin diseases (vitiligo, alopecia, and nonhealing wounds). *Stem Cells Int.* 2017;2017:4740709.
44. Schmidt B, Horsley V. Unravelling hair follicle-adipocyte communication. *Exp Dermatol.* 2012;21:827–830.
45. Kost Y, Muskat A, Mhaimeed N, et al. Exosome therapy in hair regeneration: a literature review of the evidence, challenges, and future opportunities. *J Cosmet Dermatol.* 2022;21:3226–3231.
46. Ku YC, Omer Sulaiman H, Anderson SR, et al. The potential role of exosomes in aesthetic plastic surgery: a review of current literature. *Plast Reconstr Surg Glob Open.* 2023;11:e5051.
47. Huang J, Xiong J, Yang L, et al. Cell-free exosome-laden scaffolds for tissue repair. *Nanoscale.* 2021;13:8740–8750.
48. Roets B. Potential application of PBM use in hair follicle organoid culture for the treatment of androgenic alopecia. *Mater Today Bio.* 2023;23:100851.
49. Asakawa K, Toyoshima K-ei, Ishibashi N, et al. Hair organ regeneration via the bioengineered hair follicular unit transplantation. *Sci Rep.* 2012;2:424.
50. Guarro G, Cozzani F, Rossini M, et al. The modified TIME-H scoring system, a versatile tool in wound management practice: a preliminary report. *Acta Biomed.* 2021;92:e2021226.
51. Guarro G, Cozzani F, Rossini M, et al. Wounds morphologic assessment: application and reproducibility of a virtual measuring system, pilot study. *Acta Biomed.* 2021;92:e2021227.
52. Winter E, Glauser G, Caplan IF, et al. The LACE+ index as a predictor of 30-day patient outcomes in a plastic surgery population: a coarsened exact match study. *Plast Reconstr Surg.* 2020;146:296e–305e.
53. Rehnke RD, Schusterman MA, Clarke JM, et al. Breast Reconstruction using a three-dimensional absorbable mesh scaffold and autologous fat grafting: a composite strategy based on tissue-engineering principles. *Plast Reconstr Surg.* 2020;146:409e–413e.