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Examining the Uncertainties Surrounding Exosome Therapy in Androgenetic Alopecia: A Call for Evidence-Based Practice

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ABSTRACT

Hair loss, a pervasive and often distressing condition, affects a substantial number of individuals globally. Although conventional treatments such as hair transplantation, topicals, oral medications, and injectables exist, they have limitations, including the necessity for repeated treatments, potential adverse effects, and cost barriers. Exosome therapy, an innovative and burgeoning option within regenerative medicine, offers a novel approach to hair loss treatment. Exosomes are small vesicles that are produced from the membranes of late-endosomes and secreted by cells, playing a crucial role in intercellular communication. Research on humans is limited,[1-4] and animal studies have shown that exosomes derived from various cell types can stimulate hair growth, resulting in increased research and development of exosome therapy for hair loss.[5] Establishing a uniform reporting method for exosome therapy is vital as research in this area continues to expand. A standardized approach to research reporting and results is essential for comprehending the underlying mechanisms, safety, and efficacy of exosome therapy. This article provides an in-depth analysis of the current state of exosome therapy for hair loss, including potential advantages, and limitations, as well as directions for future research.

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INTRODUCTION

Understanding Exosome Therapy

Exosome therapy represents a cutting-edge approach in regenerative medicine, leveraging the potential of exosomes derived from optimal cellular environments to achieve specific therapeutic effects in target areas. In the context of hair loss, the objective is to stimulate hair growth by harnessing exosomes carrying signaling molecules or genetic material known to promote hair follicle development, growth, and maintenance.[6]

To commence exosome therapy, the desired exosomes are isolated from a tissue source expressing high levels of target signaling molecules. Tissue sources can include human tissues such as adipose tissue, bone marrow, placenta, umbilical cord, and foreskin, or animal tissues such as porcine or murine adipose tissue, bone marrow, or bovine milk. The choice of tissue source depends on the target signaling molecules, desired therapeutic application, as well as ethical, safety, and regulatory considerations.

Following the selection of an appropriate tissue source, the tissue is processed to extract the target exosomes with optimum quality and purity ensured. This step involves the utilization of quantification and qualification methods, including but not limited to electron microscopy, reverse transcription-polymerase chain reaction, and western blotting. Careful selection of tissue sources and stringent quality control measures during exosome extraction enable researchers to develop more effective and targeted exosome therapies for various medical conditions, including hair loss.

Exosome therapy for hair regrowth is based on the principle that exosomes derived from optimal cellular environments can induce specific effects on hair follicles. Upon being introduced into the scalp, exosomes containing signaling molecules or genetic material associated with hair growth are transferred to hair follicle cells, promoting hair growth by encouraging cell proliferation, differentiation, and survival.[2]

Exosomes utilized for hair regrowth may contain various signaling molecules involved in hair follicle development, growth, and maintenance. These can include growth factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), insulin-like growth factor (IGF-1), and keratinocyte growth factor (KGF), as well as signaling pathways like wingless-related integration site (Wnt) /β-catenin, Sonic hedgehog (Shh), and bone morphogenetic protein (BMP).[3] When introduced into the scalp, these signaling molecules

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are transferred to hair follicle cells, stimulating hair growth by promoting cell proliferation, differentiation, and survival.

Moreover, growth factors such as IGF-1, KGF, and VEGF can enhance hair growth by improving blood flow to hair follicles and supplying essential nutrients and oxygen.[4] These factors can also stimulate the production of extracellular matrix components, offering structural support to hair follicles and maintaining their integrity.

In conclusion, exosome therapy holds significant potential for hair loss treatment, offering a novel and innovative solution to a prevalent and distressing condition. The advancement of exosome therapy hinges on further research to elucidate its mechanisms of action, long-term effects, and the development of a standardized approach for reporting study results.

Quality of Studies on Exosome Therapy for Hair Loss

While numerous studies have explored the potential benefits of exosome therapy for hair loss in mice, and a few in vitro studies on human hair dermal papilla cells and hair follicles have been conducted, there are currently minimal published human studies.[1-3] One study utilizing exosomes in human subjects has recently commenced in Isfahan, Iran; however, the current evidence supporting the use of exosome therapy for hair loss remains limited.[7] Given the lack of human studies, it is crucial to exercise caution in interpreting results from animal studies and in vitro studies, as they may not always be directly translatable to humans. Additionally, the methodologies used in these studies vary greatly, making it challenging to compare results and draw conclusions regarding the overall efficacy of exosome therapy for hair loss.

It is essential to address the claims made by some practitioners about the long-lasting effects of a single or limited treatment with exosome therapy. To date, these claims have not been substantiated by research. Long-term studies are necessary to determine the maintenance of treatment effects, and the scientific community should emphasize the importance of such research.

This underscores the importance of standardizing research methodologies and conducting well-designed clinical trials to establish the safety and efficacy of exosome therapy for hair loss in humans. Until more robust evidence is available, it is likely premature to recommend exosome therapy for hair loss to patients. Further research is necessary to determine the optimal dosing, duration of treatment, and safety profile of exosome therapy for hair loss.

Standardization of Exosome Therapy Production and Reporting

Standardization is critical for ensuring the safe and effective use of exosome therapy. The process of obtaining exosomes can vary significantly depending on the source. Autologous exosomes, taken from and given to the same patient, may not require the same level of processing as allogenic exosomes, which are pre-made and ready to use. Pre-made exosome kits, marketed as exosome therapy, can raise concerns due to their often lacking transparency regarding the source and contents of the exosomes. The limited disclosure of the exact contents and potential side effects of these exosomes could pose a significant risk to patients and may lead to life-threatening responses.[2] For these reasons, the use of exosome therapy products outside of federally registered clinical trials is currently illegal in the United States. It is essential for clinicians to understand the contents and effects of exosomes before administering them to patients.

Efforts have been made to standardize exosome therapy production and administration. In 2014, the International Society for Extracellular Vesicles (ISEV) proposed Minimal Information for Studies of Extracellular Vesicles ("MISEV") guidelines, which were further updated in 2018. These contained recommendations on the most appropriate methods of extracellular vesicle isolation, characterization, and reporting. The National Institute of Standards and Technology (NIST) developed reference materials to be used for extracellular vesicle development and reporting. We propose standardized reporting guidelines to be used for exosome therapy research (Table 1) that can help accelerate the translation of exosome-based therapies from laboratories to the clinic.[8,9]

Exosome Signaling Molecules for Hair Loss

Despite FDA regulations on the use of exosomes in human subjects, research into their use for hair loss continues. In hair loss research, exosomes often contain signaling molecules involved in promoting hair growth, such as β-catenin, Norrin, Fzd4, Shh, IGF-1, KGF, HGF, Wnt, BMP, miR-22-5p, miR-218-5p, and others (Table 2).[10] Autologously derived exosomes are frequently injected into the scalps of laboratory rodents, where they can deliver growth factors and other therapeutic molecules to hair follicles, demonstrating promising results in stimulating new hair growth.

Importance of Creating a Uniform Reporting Method for Exosome Therapy

As research on the potential use of exosome therapy expands, it is crucial to establish a uniform reporting method for research in this area. A standardized approach to reporting research results and patient outcomes will provide a more comprehensive and accurate understanding of the benefits and limitations of exosome therapy, as well as facilitate the development of evidence-based guidelines for treating hair loss with exosome therapy. A uniform reporting method will also promote transparency and consistency in the field, enabling accurate comparison of results across different studies. This will help identify and address any disparities in research quality

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TABLE 1.

Standardized Reporting Guidelines	
Section	**Guidelines**
Study Design and Population	1. Provide detailed information on the study design (control groups, blinding, randomization) 2. Specify target population (age, sex, ethnicity) 3. Define type and stage of hair loss 4. Report sample size and rationale
Exosome Source and Isolation	5. Describe source of exosomes and type of donor cells 6.Detail isolation methods and protocols 7. State characterization methods used to confirm exosome presence and purity
Exosome Characterization and QC	8. Report presence and relative abundance of key signaling molecules 9. Describe quality control measures to ensure consistency and potency
Intervention and Administration	10. Specify route of administration and frequency/duration of treatment 11. Describe dose of exosomes and rationale for selection 12. Detail co-treatments or adjunct therapies
Outcome Measures and Evaluation	13. Define primary and secondary outcome measures 14. Detail methods and instruments used to assess outcomes 15. Specify time points for assessments and rationale
Safety and Adverse Events	16. Report observed adverse events or side effects (severity, duration, relationship to therapy) 17. Describe safety monitoring procedures and risk mitigation strategies
Statistical Analysis	18. Detail statistical methods used to analyze data, including subgroup/sensitivity analyses 19. Report effect sizes, confidence intervals, and *P*-values for all outcome measures
Results and Interpretation	20. Present results clearly using tables, figures, or graphs 21. Discuss findings in context of existing literature and study limitations 22. Address potential biases or confounding factors
Transparency and Data Sharing	23. Encourage open access to the study protocol, data, and relevant materials 24. Consider registering the study in a public registry or repository for data sharing and collaboration

QC: Quality Control

TABLE 2.

Key Signaling Molecules and Their Roles in Hair Follicle Development and Growth	
Signaling Molecule	**Role in Hair Growth**
β-catenin	Involved in the Wnt signaling pathway, which plays a crucial role in hair follicle development and cycling. It is required for the initiation of hair follicle growth and the maintenance of hair follicle stem cells.
Norrin	A secreted protein that binds to Fzd4 and activates the Wnt/β-catenin signaling pathway, promoting hair follicle morphogenesis, growth, and maintenance.
Fzd4	A receptor for Norrin and Wnt ligands, involved in the activation of the Wnt/β-catenin signaling pathway, which is essential for hair follicle development and cycling.
Shh (Sonic Hedgehog)	A morphogen involved in hair follicle development and the regulation of hair follicle growth. It stimulates the proliferation and differentiation of hair follicle cells and promotes the anagen phase of the hair cycle.
IGF-1 (Insulin-like Growth Factor 1)	Stimulates hair follicle growth by promoting cell proliferation, differentiation, and migration in hair follicles. It also extends the anagen phase of the hair cycle and enhances the hair shaft diameter.
KGF (Keratinocyte Growth Factor)	Stimulates the growth and differentiation of keratinocytes, which are critical for hair follicle structure and function. It promotes hair growth by prolonging the anagen phase and improving the hair shaft diameter.
HGF (Hepatocyte Growth Factor)	Promotes hair follicle growth by stimulating the proliferation and differentiation of hair follicle cells. It also acts as a mitogen for hair follicle dermal papilla cells and contributes to the hair cycle progression.
Wnt	A family of secreted proteins that play a crucial role in hair follicle development and cycling through the activation of the Wnt/β-catenin signaling pathway. They regulate hair follicle stem cell maintenance, proliferation, and differentiation.
BMP (Bone Morphogenetic Protein)	Regulates hair follicle development, cycling, and stem cell maintenance. BMP signaling inhibits hair follicle growth, and its suppression is required for the anagen phase initiation and maintenance.
miR-22-5p	A microRNA that modulates gene expression in hair follicle cells. It promotes hair growth by targeting and suppressing negative regulators of the Wnt/β-catenin and BMP signaling pathways, which are critical for hair follicle development and cycling.

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TABLE 3.

Studies Utilizing Exosomes for Androgenetic Alopecia in Humans

Author, Year	Study Design	Condition	Sample Size (Male/ Female)	Age (Mean±STDev)	Intervention	Protocol	Duration	Outcomes
L. Dehghani, 2023	RCT (Recruiting)	AGA	20	Range: 25–65	Donated human amniotic mesenchymal stem cells	4 Sessions, one session every 2 weeks	2 months	Pending Completion
BS. Park; HI. Choi; G. Huh[1]	Retrospective Analysis	AGA	39 (27/12)	42.5 years (range 20–66)	ASC-exosome (AAPE® version 2.0, Prostemics, Seoul, Korea), positive for the three exosome markers, CD63, CD9, and CD81	Topical Application with microneedling, weekly	12 weeks	Mean Hair Density: 121.7 ± 37.2 to 146.6 ± 39.5 hairs/cm^2 ($p < 0.001$); Mean Hair Diameter: 52.6 ± 10.4 to 61.4 ± 10.7 μm ($p < 0.001$)
C. Huh & B. Park, 2019[2]	Pilot Study	AGA	20 (?/?)	41.9 ± 13.4 years old	Exosome	--	12 weeks	Hair Density: 105.4 to 122.7 hairs/cm^2 ($P < 0.001$); Hair Diameter: 57.5 to 64.0 mm ($P < 0.001$)
J. Zhuang; C. Youbai; J. Hu, 2022[3]	Case Report	Anaphylaxis 2/2 Exosome therapy	1 (0/1)	32 years old	Stem Cell Exosomes; Adipose-derived stem cells (ADSC)-derived exosomes (ADSC-exos)	--	--	Resolution of allergic reaction with injection of 9 ml 2% lidocaine, 1 ml 1% 5-FU, 0.1 mg triamcinolone acetonide, and drug injection treatment in the afternoon of July 1. A volume of 1 ml was injected into the forehead, 0.3 ml was injected into the nose, and 1 ml was injected into bilateral retroauricular lymph nodes

AGA: Androgenetic Alopecia

and reliability, allowing for a more accurate assessment of the overall state of the field. Moreover, a uniform reporting method will ensure that patients receive the best possible care by providing healthcare providers with a clear and comprehensive understanding of the benefits and limitations of exosome therapy. This will also help to minimize the risks associated with exosome therapy and promote the development of safe and effective treatments for hair loss.

CONCLUSION

The potential of exosome therapy as a new treatment option for hair loss is promising, however, requires further research and development to fully comprehend its benefits and limitations. One aspect to consider is the current absence of Food and Drugs Administration (FDA)-approved exosome products. In 2019 and reiterated in 2020, the FDA issued a statement warning that exosomes are not approved, nor have they been proven effective, in response to reports of five patients experiencing serious adverse events, including infection and sepsis, within two months of being treated with exosome products.

To advance the field of exosome therapy, it is critical to establish a standardized approach to reporting research and patient outcomes. This will facilitate the development of evidence-based guidelines, support the safe and effective use of exosome therapy, and provide a comprehensive and accurate understanding of the therapy's efficacy. While the current state of exosome therapy research is still in its early stages, future studies must focus on several important factors, including the composition and source of exosomes, the mechanism of action in promoting hair growth, and the long-term effects of exosome therapy.

It is imperative that we establish proper reporting methods and standardization in classifying exosome treatments. This will enable effective comparison and analysis of future studies, leading to a better understanding of the therapy and its effectiveness, and ultimately ensuring the safe and successful use of exosome therapy for hair loss.

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DISCLOSURES

Dr Shapiro is a consultant for Pfizer, Eli Lilly, Eirion, Follica, and Replicel Life Sciences. Drs Shapiro and Lo Sicco have been investigators for Regen Lab and are investigators for Pfizer. Dr Lo Sicco is a consultant for Pfizer and Aquis. MGB, LA, and MI have no conflicts to disclose.

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