

REVIEW

Exosomes: A New Effective Non-Surgical Therapy for Androgenetic Alopecia?

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ABSTRACT

Exosome therapy is a promising new approach for the treatment of hair loss. Current treatments for androgenetic alopecia, the most common form of hair loss, fall short of providing satisfactory efficacy with minimal side effects; thus, the fact that exosome therapy delivers impressive hair growth with no reported adverse events makes this therapy an attractive avenue to be explored; nevertheless, due to the novelty of this treatment, clinical trials to confirm its efficacy and safety are lacking. The current state of knowledge that is publicly available on the efficacy of exosome therapy for treatment of hair loss is reviewed, and the potential of exosomes as an alternate therapy for hair restoration is discussed. (*SKINmed*. 2020;18:96–100)

Androgenetic alopecia (AGA) is a common progressive hair loss disorder that affects both men and women, with onset and severity increasing with age. A significant feature of AGA is follicular miniaturization where terminal hair gets replaced by vellus hair.¹ As the condition advances, these miniaturized follicles eventually become dormant and, in severe patients, can progress to follicular deletion.² To date, hair restoration therapies stimulate hair growth, in part, by inducing hair follicles to progress from telogen to anagen phase, causing miniaturized hair follicles to once again produce terminal hair;³ nevertheless, in patients with severe AGA, the majority of miniaturized follicles become dormant or have dissipated, rendering treatment ineffective.² For years, scientists have sought to identify ways to restore dormant follicles, or generate new follicles, as an effective means to stimulate hair growth.

Exosomes were first thought to be cellular waste products but are now known to be vital for intercellular communication and can modulate a variety of cell and tissue functions, including angiogenesis, immune responses, and cellular proliferation and differentiation.⁴ This discovery sparked the exploration of the therapeutic potential of exosomes, with exciting findings in neurologic diseases, cardiovascular disease, and kidney disease, and many believe that this therapy will revolutionize regenerative

medicine;⁴ furthermore, the use of injectable exosomes has generated excitement in the field of hair restoration. Some hair restoration surgeons are now marketing this new therapy as impressively effective, with visible results attained more rapidly than conventional treatments;^{5–10} however, publicly available data supporting these claims are lacking. Here, a literature review is presented to examine the available data on the effectiveness and safety of exosome therapy for promoting hair growth, and the potential of exosomes as an alternative therapy for hair restoration is discussed.

LITERATURE SEARCH

A literature search was conducted on January 20, 2020 using PubMed Central with the search syntax “exosome” and “hair growth,” which retrieved 51 studies. After title and abstract screening, 16 studies were deemed relevant. One additional study was found through reference mining and another through searching conference proceedings of the *Journal of the American Academy of Dermatology*; thus, 18 studies were included for discussion in this review.

Two clinical trial databases, clinicaltrials.gov and clinicaltrialsregister.eu, were searched using the term “exosome,” and all results were screened for any trials mentioning hair. The search

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was conducted on January 20, 2020, and no clinical trials investigating the effects of exosomes on hair restoration or hair growth were found.

IN VITRO STUDIES

Dermal papilla (DP) cells are mesenchymal-derived cells located at the base of the hair follicle and play a critical role in growth and cycling of hair follicles.¹¹ Development and function of hair follicles are highly dependent on signaling between epithelial and DP cells through the *Wnt*/β-catenin signaling pathway,^{12–14} thus, many *in vitro* studies have quantified factors associated with the *Wnt*/β-catenin pathway using DP cells as an experimental model as evidence reflective of hair growth. Additionally, studies have used a variety of cell types from which to isolate exosomes or conditioned media, including mesenchymal stem cells, adipose-derived stem cells, dermal fibroblast cultures and DP cell cultures.

The modulatory properties of exosomes on hair growth *in vitro* were first noted in studies using stem cell-conditioned media. For example, conditioned media from deer antler mesenchymal stem cells increased *Wnt3a* mRNA expression in DP cells, resulting in enhanced proliferation of these cells compared to controls (3.2-fold).¹⁵ The researchers then treated DP cells with extracellular vesicles isolated from the deer antler mesenchymal stem cell-conditioned media and observed an even greater induction of *Wnt3a* expression (eightfold), suggesting that the extracellular vesicles were the active compound in conditioned media that induced *Wnt3a* expression. In another study, extracellular vesicles isolated from media conditioned by mouse-bone marrow mesenchymal stem cells increased proliferation, migration, as well as expression and release of growth factors in human DP cells.¹⁶

Other studies have shown that media conditioned by adipose-derived stem cells increased proliferation of both DP cells^{17–19} and epidermal keratinocytes.^{17,19} Enhanced proliferation of these cells was associated with increased expression of genes associated with hair growth, such as transforming growth factor β-2 and noggin,¹⁸ as well as Erk and Akt.¹⁹ Whether these effects were due to exosomes present in the conditioned media or not was not investigated in these studies.

Exosomes isolated from DP cells increase proliferation of DP cells,²⁰ hair matrix cells,²¹ and outer root sheath cells.^{20,22} DP-derived exosomes also increase the migration of outer root sheath cells²² and promote hair follicle stem cell proliferation and differentiation.²³ Studies using *ex vivo*-cultured human hair follicles found that DP cell-derived exosomes increased hair shaft elongation^{20,21} and prolonged anagen phase.²¹ Similarly, exosomes isolated from activated human dermal fibroblast cultures also

enhance hair follicle growth *ex vivo*.²⁴ DP cell-derived exosomes have also been shown to increase the expression of β-catenin and Sonic Hedgehog in outer root sheath cells,²² which are the factors implicated in promoting hair follicle development.²⁵ In cultured hair follicles, DP cell-derived exosomes increase the protein expression of *Wnt3a* and β-catenin and decrease the expression of bone morphogenetic protein 2 (BMP2), which inhibits anagen initiation.^{21,26,27}

Together, these *in vitro* data support the hypothesis that exosomes derived from a variety of cell types promote hair follicle development and hair growth.

ANIMAL STUDIES

Some of the first studies to report the regenerative effects of exosomes on hair growth were focused on wound healing. For example, a study investigating wound healing in rats treated with human umbilical mesenchymal stem cell-conditioned media reported an unexpected stimulation of hair follicle development around the treated wounds;²⁸ however, this study did not investigate whether this effect was due to exosomes in the conditioned media. One study evaluated the efficacy of exosomes for wound closure and also observed unexpected enhanced hair growth in mice and minipigs, sparking the notion that exosome therapy could have potential as a hair loss therapy.²⁹

Subsequent studies have directly tested the effect of exosomes on hair growth *in vivo*. One study used an intradermal injection of mesenchymal stem cell-derived extracellular vesicles in mice and observed a more rapid transition from telogen to anagen and increased expression of *Wnt3a* and *Wnt5a* in exosome-treated mice compared to vehicle-treated controls. This study also revealed that minoxidil treatment and exosome treatment had very similar results: complete hair regrowth in shaved mice by day 27, whereas control mice only showed faint hair regrowth.¹⁶ In addition, mice treated with media conditioned by adipose-derived stem cells or exosomes isolated from human bone marrow mesenchymal stem cells display increased progression from telogen to anagen phase and increased hair regeneration in a significantly shorter period than non-treated animals.^{17,18,30}

Intradermal injections of exosomes isolated from DP cells also accelerated the onset of anagen from telogen,^{20–22} prolonged anagen phase,²⁰ and delayed catagen²² in shaved mice. Exosome treatment augmented hair follicle neogenesis when DP spheres and epidermal cells were co-implanted into mice.²⁰

Collectively, these data strongly suggest that exosomes have the ability to promote hair growth and hair regeneration at an accelerated rate in experimental animals.

HUMAN STUDIES

Although mostly anecdotal to date, exosome therapy has shown promising results in humans as well. The most enticing result reported by hair restoration surgeons is visible hair growth much earlier than conventional nonsurgical therapies (Figure 1). Even so, using our search criteria, we only found one article in which the effects of exosomes on hair restoration in humans were evaluated. In this study, hair density and thickness were measured at start of treatment and 12 weeks after exosome treatment in 20 patients with AGA. The researchers reported that exosome therapy increased mean hair density from 105.5 to 122.7 hairs/cm² ($P < 0.001$) and mean hair thickness from 57.5 to 64.0 μm ($P < 0.001$) from baseline to assessment at week 12, respectively.³¹ The researchers also stated that patients reported no serious adverse events. A number of other studies have shown similar effects in AGA patients treated with media conditioned by adipose-derived stem cells; however, whether these effects are due to the presence of exosomes in the conditioned media is not known.^{32–35}



Figure 1. Effect of exosome treatment on hair restoration. Photographs of two patients at start of treatment and (a) 1 month and (b) 3 months after treatment with a single injection of exosomes.⁸

DISCUSSION

Research into exosome therapy for hair restoration is a fascinating new field, and hair restoration surgeons have largely agreed that this treatment has major potential; however, publicly available trials investigating the efficacy and safety of this treatment in humans are lacking. Recently, the US Food and Drug Administration (FDA) issued a warning about the use of exosome therapy in general, stating that there are currently no FDA-approved exosome products and that the public should be aware “of multiple recent reports of serious adverse events experienced by patients in Nebraska.”³⁶ This advisory highlights the need for clinical trials to appropriately test the safety and efficacy of this novel therapy. Clinical trials are also important for determining the best way to manufacture this product and apply this therapy.

The current FDA-approved therapies for hair restoration include topical minoxidil and oral finasteride; however, both have significant limitations. Although topical minoxidil is approved for use in men and women, discontinuation of this treatment is common due to several unwanted side effects, unsatisfactory effectiveness, and the need for continual application. Oral finasteride is only approved for AGA treatment in men due to its teratogenic potential, but has several unpleasant sexual side effects, such as decreased libido, impotency, and ejaculation disorders,³⁷ that often dissuade patients from using it. Considering that hair loss can have a significant impact on self-image and mental health,^{38,39} identification of novel and effective treatments with minimal adverse effects is needed.

Hair follicle growth and cycling is regulated by paracrine crosstalk between epithelial cells and mesenchymal DP cells,^{12,24,40} which is disrupted in AGA.⁴¹ Additionally, embryonic hair follicle morphogenesis is also coordinated by mesenchymal–epithelial interactions.⁴² Together, these data suggest that paracrine communication between mesenchymal DP cells and epithelial cells is important for maintaining follicular homeostasis and establishing follicular neogenesis. Exosomes are an integral component of paracrine signaling and relay communication through cell–cell transfer of proteins, messenger ribonucleic acid (mRNA), and micro ribonucleic acid (miRNA);⁴³ thus, exosome therapy may promote hair growth by providing the signals needed to reinstate or initiate mesenchymal–epithelial crosstalk, leading to restoration of miniaturized hair follicles and follicular neogenesis, respectively.

CONCLUSIONS

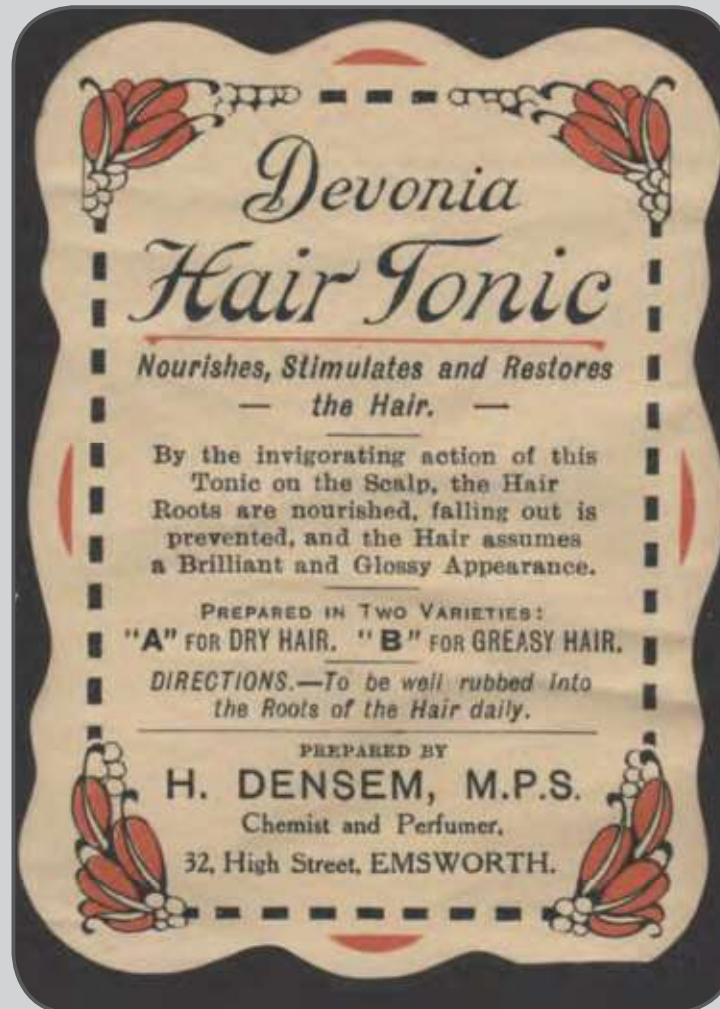
The marked hair growth at an earlier-than-expected timeline and lack of adverse events elicited by exosome therapy are promising and merit further study to confirm its efficacy and safety in humans in a clinical trial setting. Clinical trials are also needed to determine the best way to manufacture and apply exosome therapy, and

whether different tissue sources of exosomes affect the therapeutic potential. If established, exosome therapy may become a leading therapeutic modality in nonsurgical hair restoration for AGA.

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