Current Perspectives in Aesthetics: Harnessing the Therapeutic Potential of Exosomes for Skin Rejuvenation and Scar Reduction

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ABSTRACT

Background: We are learning, too, that the love of beauty is one of nature's greatest healers. Anti-ageing, skin rejuvenation, wound healing, scar mark removal and lightening the hyperpigmentation are few of the many achievable outcomes desired by aesthetic clients. Driving demand for the non-surgical cosmetic treatments has taken the limelight and thus we see effective innovations daily.

Objective: Exosomes are small extracellular Nano-vesicles that are typically 30–200 nanometers in diameter, and they contain a variety of proteins, lipids, and genetic material such as mRNA and miRNA Exosomes have use in cosmetics, skin care, tissue regeneration, and dermatological diseases such as atopic dermatitis, psoriasis, SLE, alopecia, hyperpigmentation and hypopigmentation as it has properties to regulate pigmentation. In this review we are mainly focused on the role of exosomes in skin rejuvenation and scar removal properties.

Methods: This multicenter study was conducted from Jan 2022 to July 2022. Thirty female consecutive participants were injected with exosomes in two sessions with 3 months interval. Evaluations were performed by comparing the pre-and post-improvement of skin, before after photography by participants, therapeutic physician and blindly by a second dermatologist. A search was conducted with the keywords, exosomes, stem cells, skin rejuvenation and scar removal. Exosomes term filtered by relevant subheadings was also utilized.

Results: Studies have demonstrated the therapeutic capabilities of exosomes in scar modulation and skin rejuvenation. In 3 and 6 months follow-ups respectively, moderate to excellent improvement in dark spots (44 4%, 62.9%), fine wrinkles(48.1%, 51.8%), nasolabial fold (22.2%, 33.33%) and skin rigidity (55.5%, 70.3%) reported by patients. Moderate to good improvement in dark spots (40.7%, 55.5%), fine wrinkles (51.8%, 48.1%) nasolabial folds (22.2%, 25.9%) and skin rigidity (44.4%, 59.2%) demonstrated by physician's evaluation. Moderate to good improvement in dark spots (37.0%, 48.1%), fine wrinkles (29.6%, 40.7%) nasolabial folds (18.5%, 14.8%) and skin rigidity (48.1%, 59.2%) by second dermatologist.

Conclusion: In summary, exosome-based therapies, with their ability to regulate gene expression in pigmentation and facilitate efficient melanin transfer between cells, present a dynamic frontier in medicine. Operating in a paracrine manner, exosomes modulate skin cell interactions, showcasing their potential for practical applications in regenerative medicine across diverse diseases.

Keywords: _exosomes, skin rejuvenation, scar reduction,

(Citation:Khan Saba, Shaikh Fazal Bilal , Memon Aaisha , Shaikh BilalRaheela, Abbas Zafar Syed) MC 2023, 23 (1) 45-52

ARTICLE INFORMATION

Received on: 28-01-2022
Correction: 9-7-2022
Accepted: 15-7-2022

Authors Contribution:
1. Conceptualization, methodology design, data analysis, and critical manuscript revision.
2. Data interpretation, manuscript drafting, and critical manuscript revision.
3. Revision, correction of language, reference cross-check.
4. Data collection, literature review, and manuscript drafting.
5. Statistical analysis, interpretation of results, and manuscript revision.
6. Patient record management, data analysis, and critical manuscript review.

Funding Statement
This study did not receive any specific grant from any funding agency or non-profit organization.

Conflicts of Interest
The authors have no conflicts of interest in this work

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INTRODUCTION

Aging of the human body is inevitable with increasing age and is first observed easily in the skin, which is the largest and most superficial organ in the human body. [1,2,3,4]. Exosomes are a type of extracellular vesicle[5]., typically between 30-160nm in size that are secreted from multiple cell types (e.g., blood cells, endothelial cells, immunocytes, platelets, etc.) [6] and fluids (e.g., saliva, blood, cerebrospinal fluid, breast milk, etc.) [7]. Exosomes are unique from other micro vesicles not just because of their small size, but because they contain both intracellular and extracellular components of the source cell. An exosome consists of a protective lipid bilayer [7,9] that contains variable cargo, including DNA, MRNA, microRNA (miRNA), cytokines, and cytoplasmic proteins. Exosome production is enhanced under periods of cellular stress [8,10,11] and plays an important role in cell-to-cell communication and immune regulation [8,12].

Exosome are formed when the cell membrane undergoes endocytosis, creating an endosome. The endosome then creates multiple small vesicles by invaginating parts of the endosomal membrane and is now termed a multivesicular body (MVB). Not well understood is how the various cargos are sorted into the intraluminal vesicles from the Trans Golgi network, endoplasmic reticulum, and other organelles [8,13]. The intraluminal vesicle can include nucleic acids, proteins, lipids, cytokines, transcription factor receptors, mRNA, DNA and miRNA [8,12,14,15]. Not all intraluminal vesicles are released as exosomes, some MVBs may fuse with lysosomes or auto phagosomes to be degraded. However, if the MVB fuses with the cell membrane and releases the intraluminal vesicles, those vesicles are now termed "exosomes."

Exosomes, on account of their appropriate size and property along with their evident role in numerous pathobiological processes, the potential of exosomes therapy in the management of various neurodegenerative disorders, infectious diseases, musculoskeletal disorders and cardiovascular disorders is overwhelming. Hence the recent introduction of exosomes derived from stem cells in conditioned media into the skin rejuvenation space. Other types of stem cell derived extracellular vesicles (SC-EVs) have also been found to have a role in anti-aging [16]. For instance, exosomes derived from human umbilical cord blood mesenchymal stem cells (UCB-MSCs) have been demonstrated to promote cell migration and collagen synthesis of human dermal fibroblasts (HDFs) [17]. The same group found that these UCB-MSCs-derived exosomes permeated the skin layer and were found to increase the synthesis of collagen and elastin, the major building blocks of skin rejuvenation.

Exosomes are recently gaining attention in the cosmetic dermatology [18] and are now being used in injectable forms, for micro needling serums as well as in topical serums and creams. As medical breakthroughs continue to occur and revolutionize the field, the power of the exosome keeps offering more and more opportunities for people in the medical field everywhere. With regenerative medicine proving it self to be more powerful than typical drugs or treatment, never before has there been a better choice for combating the aging process along with a variety of medical conditions. The self-care trend is partly driven by the idea that people should take care of their skin since it's the largest organ in the body and the rising popularity of social media has played major role. Products like facial moisturizers, serums, and masks are becoming more popular, as they provide a way to nourish and protect the skin from environmental damage. This has helped to create a demand for products that can help individuals achieve a certain look or level of beauty.

Exosomes have been found to be beneficial for skin care, as they are filled with molecules that help stimulate collagen production, exosomes can help to reduce wrinkles and fine lines [19], help hydration and the protection of the skin. These molecules can help to boost collagen production, reduce inflammation, and protect the skin. Additionally, exosomes can help to repair skin damage such as sun damage and acne scars. Exosomes proteins and lipids can help to plump and hydrate the skin, which can help to improve skin texture. Ingredients of exosomes such as cytokines, nucleic acids, proteins, and other bioactive compounds can also help to protect the skin from environmental stressors and reduce the appearance of dark spots and other discoloration. With their ability to help improve skin tone, texture and appearance exosomes provide several promising therapeutic and anti-aging

benefits. They contain miRNAs that are proven to regulate gene expression in the cells around the wound. This promotes the formation of new blood vessels, increases the blood flow to the wound site. This increased blood flow then delivers oxygen and nutrients to the wound which further speeds up healing process [20]. Adipose-derived stem cells (ASCs) and their exosomes have been shown to have a therapeutic role in treating aberrant skin conditions, including wound healing, acne and alopecia. ASC-exosomes have been shown to reduce inflammation and increase the production of extracellular matrix and growth factors, resulting in improved skin quality. Overall, the unique properties of exosomes, including their anti-inflammatory and immunomodulatory properties, their ability to promote angiogenesis and wound healing and their potential to promote skin regeneration, make them an attractive option for reconstructive surgery.

Exosomes released from keratinocytes have been found to contain anti-inflammatory mediators such as transforming growth factor beta (TGF-B), which can suppress the activation of T cells and reduce inflammation. Exosomes released from mast cells can also contain regulatory cytokines such as 1L-10 and TGF-B, which can suppress the activation of T cells and reduce inflammation. In addition, exosomes have been found to contain immune modulatory molecules such as microRNAs that are shown to regulate the expression of genes involved in immune responses. For example exosomes released from mast cells have been found to contain microRNAs that stimulate the downregulation of pro-inflammatory cytokines expressions such as IL-4 and IL-13 which have been shown to reduce inflammation. Studies have demonstrated that these exosomes can reduce inflammation and promote skin barrier restoration by increasing ceramide and dihydroceramide production. This suggests ASC-exosomes could be a viable treatment option for Atopic Dermatitis, as there are limited available treatments. Therefore, this cell-free theory could provide much needed relief for those suffering from this condition [21]. In clinical studies, exosomes therapy has also been found to be safe and effective for scar removal. It can reduce the appearance of scars, improve skin hydration and elasticity, and reduce inflammation. It can also help to strengthen the skin's natural defenses against infection. Recent studies have identified that exosomes may play an important role in the regulation of pigmentation in multiple organisms, including humans, through several different mechanisms. Exosomes have been shown to regulate the expression of genes involved in pigmentation and provide an efficient way for cells to transfer melanin-producing enzymes to other cells, enabling them to synthesize and produce melanin [22]. Additionally, exosomes can regulate the expression of tyrosinase, which is important for modulating the production of melanin. Keratinocytes-derived exosomes have been shown to activate melanocyte precursors and induce their differentiation into mature melanocytes. Furthermore, exosomes can help to stimulate the migration of melanocytes to areas of the skin where pigment production is needed. Findings suggest that Exosomes derived from DP cells can promote hair growth and regeneration by regulating the activity of follicular dermal and epidermal cells. These results have implications for the development of therapeutic strategies for hair loss

MATERIAL AND METHODS

In this multi-center prospective investigating study, 30 female consecutive participants with Glogau skin score (6) of II to IV, were recruited. The exclusion criteria were as follows: pregnant or lactating women, patients with severe diabetes, hypertension, or cardiopulmonary insufficiency and patients with a bleeding tendency or coagulation disorders. Patients who received chemical peel, dermabrasion, soft tissue filler, botulinum toxin injection, mesotherapy or other resurfacing surgeries and patients who have taken isotretinoin, vitamin A, vitamin C or medications that affect collagen synthesis were excluded.

After collecting photos and writing medical records, the facial treatment areas were coated with anesthetic cream Emla for half an hour. The stem cell derived exosomes was prepared according to standard procedures. Exosomes were in lyophilized powder form and were activated by adding 5ml of 0.9% normal saline in the ampule, dissolving sufficiently by lightly shaking the mixture 3~4 times. The solution was poured on the desired skin area to

let get absorbed, micro needling and injection techniques were also used as per requirement in a sterile condition. Digital photos of patients were collected 3 and 6 months after the treatment. Evaluation of wrinkle and dark spots improvement was performed on the basis of personal judgment of participants, by comparing the pre-and post-improvement of skin, observation of before and after improvement photography by therapeutic physician and a second dermatologist who was unaware of the order of photos. All data was collected through predesigned proforma.

RESULTS

27 out of 30 participants completed the study. One patient, due to pain did not continue the trial and 2 more patients due to loss of follow up were omitted from the study. Mean age of patients was 38 to 56 years and in the range of 21 to 62 years.17 patients (62.9%) had glogou score II, 9 patients (33.3%) glogou II and 1 patient (3.70%) glogou IV. The results were evaluated 3 and 6 months after the last session by comparing the pre-and post-improvement of skin, by the final patients' satisfaction questionnaire, by the physician's impressions and double blind evaluation of pre and post treatment photographs by another dermatologist.

TABLE 1

No. of Patients	Therapy	Condition	Assessment Period	Mean Age/Range (Years)
23	Exosomes monotherapy	Facial aging	6 months	34-62
7	Exosomes monotherapy	Facial scar marks	6 months	21-56

DISCUSSION

As life progresses, physical changes in the skin are the first observation evidencing organismal aging. Since the ancient times, people have strived to improve the quality of their skin through anti-aging treatments. In the present days, the skin has an important part in social lives boosting self-esteem and self-consistency. Therefore, various anti-aging treatments have been introduced in the cosmetic industry [23]. The cosmetics industry is constantly evolving as it is driven by consumer demand for new and innovative products. Exosomes have been identified as potential new ingredients in cosmetics, with the potential to provide significant cosmetic benefits. Exosomes contain numerous different types of materials making them extremely promising in the field of regenerative medicine, and their lipid-bilayer membranes contain certain marker proteins that identify them specifically to particular cells. Thus, exosomes are important players in cell-to-cell communication. According to our study the therapeutic capabilities of exosomes in scar modulation and skin rejuvenation showed these results in 3 and 6 months follow-ups respectively, moderate to excellent improvement in dark spots (44.4%,74.0%), fine wrinkles (55.5%,70.3%), nasolabial fold (22.2%, 44.4%), and skin rigidity (59.2%, 77.7%) reported by patients. Moderate to excellent improvement in dark spots (40.7%, 59.2%), fine wrinkles (51.8%, 48.1%) nasolabial folds (22.2%, 33.3%) and skin rigidity (44.4%, 62.9%) demonstrated by physician's evaluation. Moderate to good improvement in darks pots (37.0%, 48.1%), fine wrinkles (29.6%, 40.7%), nasolabial folds (33.3%, 29.6%) and skin rigidity (48.1%, 59.2%) by second dermatologist. No serious or persistent side effects were reported. In this study patient satisfaction score was higher than physician's score which might be due to the fact that patient detect objective improvement at an earlier stage. The strength of this study was using several ways for evaluating the results. Face rejuvenation with exosomes is a promising non-surgical technique. Best effects of exosomes were observed in

Patients' self-evaluations

Patients' satisfaction regarding dark spots, fine wrinkles, nasolabial folds and skin rigidity at 3 and 6 months after treatment with exosomes are shown in table II.

TABLE 2

Improvement		Dark spots	Fine wrinkles	Nasolabial folds	Skin rigidity
3 months after treatment	None	2(7.04)	2(7.04)	8(29.6)	1(3.70)
	Poor	5(18.5)	1(3.70)	3(29.6)	3(11.1)
	Moderate	8(29.6)	9(40.7)	7(22.2)	7(25.9)
	Excellent	12(44.4)	15(55.5)	9(11.1)	16(59.2)
6 months after treatment	None	1(3.70)	1(3.70)	4(14.8)	1(7.04)
	Poor	2(7.40)	2(7.04)	3(11.1)	1(18.5)
	Moderate	4(14.8)	5(18.5)	8(29.6)	4(14.8)
	Excellent	20(74.0)	19(70.3)	12(44.4)	21(77.7)

Evaluation of the Physician

TABLE 3

Improvement		Dark spots	Fine wrinkles	Nasolabial folds	Skin rigidity
3 months after treatment	None	2(7.04)	3(11.1)	9(33.3)	2(7.40)
	Poor	5(18.5)	2(7.40)	10(37.0)	4(14.8)
	Moderate	9(33.3)	14(51.8)	6(22.2)	9(33.3)
	Excellent	11(40.7)	8(29.6)	2(7.40)	12(44.4)
6 months after treatment	None	1(3.70)	2(7.40)	8(29.6)	1(3.70)
	Poor	2(7.40)	1(3.70)	3(11.1)	1(3.70)
	Moderate	8(29.6)	11(40.7)	7(25.9)	8(29.6)
	Excellent	16(59.2)	13(48.1)	9(33.3)	17(62.9)

Double Evaluation of the Second Dermatologist

TABLE 4

Improvement		Dark spots	Fine wrinkles	Nasolabial folds	Skin rigidity
3 months after treatment	None	5(18.5)	5(18.5)	8(29.6)	2(7.40)
	Poor	5(18.5)	7(25.9)	5(18.5)	1(14.8)
	Moderate	7(25.9)	8(29.6)	9(33.3)	13(48.1)
	Excellent	10(37.0)	7(25.9)	5(18.5)	11(40.7)
6 months after treatment	None	1(3.70)	4(14.8)	4(14.8)	1(3.70)
	Poor	2(7.40)	3(311.1)	9(33.3)	1(3.70)
	Moderate	11(40.7)	11(40.7)	8(29.6)	9(33.3)
	Excellent	13(48.1)	9(33.3)	6(22.2)	16(59.2)

improving darks pots and skin rigidity. No serious or persistent side effects were reported.

In recent years, the effects of exosomes on various skin defects have been extensively studied. The key benefits of exosomes are the high stability, non-immune rejection, and direct stimulation of target cells [24,25]. Especially, the miRNAs contained in the exosomes are engaged in the regulation of various cellular responses by binding to the 3?-untranslated region [26]. As the skin ages, various changes occur such as decrease in the collagen type-I content, disorganization of the capillary network, denaturation of elastic fibers etc. [27]. These degenerative changes may result in decreased vessel structures in the skin tissue. A proper vascularization is an essential part for a healthy skin which provides nutrient supply to the skin cells to maintain their activities. Therefore, one solution to aging skin may be solved by increasing the vascular number. Moreover, vascularization plays an important role in wound healing [28]. As mentioned before, the dermal layer is damaged due to fragmentation of collagen type-I and elastic fibers in aged skin. Therefore, rebuilding the dermal structure might result in anti-aging and wound healing of the skin. MiR-21 is known to promote keratinocyte migration and re-epithelialization in skin wound healing [29]. Studies have shown that the injection of exosomes into the skin can stimulate the production of collagen and elastin, two substances that are essential for skin regeneration [30]. As an example, exosomes derived from human dermal fibroblasts spheroids were evaluated for anti-aging purposes [31]. Kim et al. examined the effects of exosomes derived from human umbilical cord blood-derived mesenchymal stem cells (UCB-MSCs) for skin rejuvenation [32]. Among various growth factors detected in the exosomes, EGF was found in greater concentrations. When human dermal fibroblasts (HDFs) were exposed to the exosomes, collagen and elastin production was enhanced. Thus, UCB-MSCs-derived exosomes can be used to rebuild the dermal layer.

CONCLUSION:

In summary, exosome-based therapies are a dynamic and growing area of research that has the potential to disrupt multiple areas of medicine. Exosomes have been shown to regulate the expression of genes involved in pigmentation and provide an efficient way for cells to transfer melanin-producing enzymes to other cells, enabling them to synthesize and produce melanin. Exosomes primarily exert their effects in a paracrine function and modulate the interactions between keratinocytes and other cells of the skin. It is clear that exosome

use for regenerative medicine is a feasible therapeutic offering practical application for a wide range of diseases.

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