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Research Article

The Utilization of Human Placental, Fetal Mesenchymal Stem Cell Derived- Exosomes in Treating Keloid Scars

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Abstract

Objective: This pilot study examines the potential efficacy of applying exosomes to excised keloid wound beds to modify and regulate the wound healing pathway, to promote scar-free healing and reduce keloid formation and recurrence. **Method:** The effect of human placental mesenchymal stem cell derived exosomes (XoGlo; Kimera Labs, Miami, FL) was studied on 21 patients. All patients had previous excision attempts of their keloids. In each case, the keloid recurred. Under current Institutional Review Board (IRB) approval, and with proper informed consent, patients in a pilot study, had their keloids excised with a CO_2 laser, exosomes immediately administered into the wound, and coverage with an amniotic membrane graft when appropriate. All patients were followed for recurrence. **Results:** Over the 2 years of follow-up 18 of 21 patients in the pilot study with keloid scars had no recurrence. Three patients of twenty-one developed a recurrence of their keloid scars within 2 months. All were African American. There was one female recurrence of a sternal keloid, one male recurrence on the face and one male recurrence on the neck. All recurrences were in hair bearing regions on the chest, face, and neck. When the process was repeated on the 3 recurrent keloids with the addition of laser hair removal, the 3 revision cases remained recurrence free. **Conclusion:** Exosomes appear to have a benefit in reducing the recurrence of keloid scars. It is hypothesized that the positive regenerative effects of exosomes override pro-fibrotic growth factors via anti-inflammatory and anti-fibrotic growth factors, especially TGFbeta 3, IL-10, IL-12, MMP-2, MMP-9 and TNF-alpha. These play a vital role in regulating “normal” wound healing and a “scarless” healing model.

Keywords: Exosomes; Fetal mesenchymal stem cells; Keloid scar

Introduction

Hypertrophic scars and keloids are fibroproliferative disorders resulting from abnormal wound healing. There are numerous studies surrounding the three, but overlapping stages of wound healing: inflammation, proliferation, and matrix remodeling [1]. Early inflammatory cascades follow immediately post injury, during which later scar development outcomes appear to be dictated [2]. The mechanism by which prolonged inflammation promotes scarring is not known. It appears that the propensity to abnormal scarring is programmed during, and by parts of the inflammatory cascade, as shown in fetal wound healing studies [3-5]. Prolonged and excessive inflammation result within the context of increased fibroblast activity, which in turn produces excessive ECM, with an overall scar volume increase [5]. Neutrophils, matrix metalloproteinases and collagenases then infiltrate the wound. This causes tissue loss, leaving the area devoid of extracellular matrix that is then replaced with scar tissue [1]. The final remodeling stage includes the migration and proliferation of fibroblasts, collagen production and deposition, and angiogenesis [1]. There is a complex synergy between cells, which secrete growth factors, cytokines, and components of the extracellular matrix, thereby modulating collagen metabolism [6].

It is important to achieve a proper balance between these wound healing phases. Synthesis and degradation of ECM must be balanced, or wound healing can be delayed or result in abnormal scarring. Figure 1 summarizes the growth factors that enhance fibrosis, those that attenuate fibrosis, and the complex overlap of the phases of healing. The search for appropriate models to study these healing reactions in the regenerative environment has been lacking. Early wound healing studies in fetal mammals [7-11], and marsupials [12] provided insight into the cellular and molecular regulation of scar-free healing. However, comparisons of wound healing between fetal and adult mammals have biological and practical limitations. The developing fetus when it heals scar free, is in a moist, sterile environment, its cells are in a state of chronic hypoxia, has an immature endocrine system, and is immune incompetent [3]. Adult skin is completely differentiated, and open to desiccation and infection.

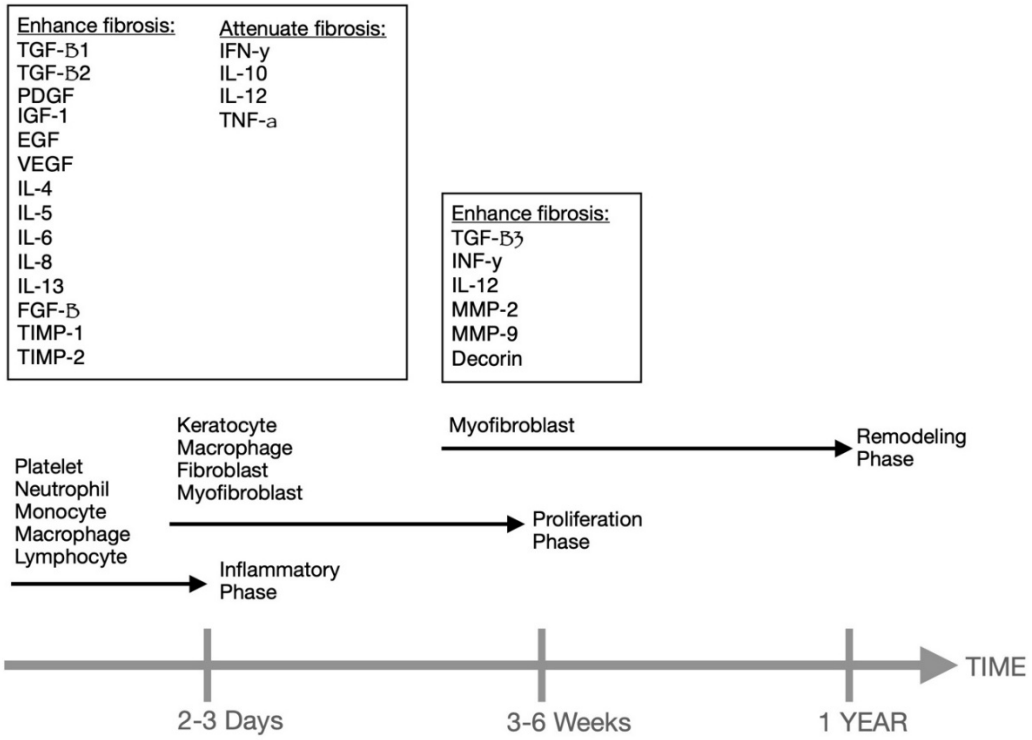

Figure 1: Cytokines involved in wound healing.

The Adult Axolotl serves as a model blueprint for scar-free healing in Vertebrates [13]. Comparing scar-free healing in terrestrial axolotls to scar formation in mammals, axolotls exhibited a reduced hemostatic response, lower neutrophil levels, reduced inflammatory response, faster re-epithelialization rate, delay in ECM production, high levels of fibronectin and tenascin-C in ECM, and regeneration of glands and dermis instead of scarring [14]. Reason suggests that if this balance could be mimicked in the adult mammal, perhaps normal healing could replace the tendency to abnormal scars, such as keloids. The fields of cellular medicine, regenerative and stem cell therapies continue to grow exponentially [14]. The effects of human placental, fetal mesenchymal stem cell derived- exosomes on aging skin have been delineated [14]. These studies have shown that with proper homing, exosomes illicit strong regenerative, immunomodulatory, anti-inflammatory, and anti-prostaglandin effects. They are also packed with the antifibrotic cytokines shown to be necessary for normal healing. The strong regenerative synergy of combining exosomes with amniotic membrane grafts [14], which accelerate re-epithelialization and reduce inflammation [15], are hypothesized to be the cornerstone to exosomes' success at reducing the formation and recurrence of keloid scars in those patients with the genetic propensity to form them. This study examines the potential benefit of human, c-section donated, cultured fetal mesenchymal stem cell-derived exosomes in the treatment of keloid scars, after excision with the carbon dioxide laser. With larger surface area excisions, or when residual healthy cartilage was exposed, tissue coverage with amniotic membrane extracellular grafts was utilized. These grafts provide a scaffold for enhanced exosome performance in larger surface areas [14].

Materials and Methods

Under current Institutional Review Board Approval from the International Cell Surgical Society (ICSS-2021-011), an initial pilot study examined the effect of human placental mesenchymal stem cell derived exosomes (XoGlo; Kimera Labs, Miami, FL) on 21 patients. Proper informed consent was obtained in all cases. There were 10 males and 11 females. There were 13 African American, 2 Asian, 2 Mediterranean, 2 Indian and 2 Caucasian patients. Ages ranged from 23 to 57 years. Keloids were excised from the facial cheek in 1 case, ear lobules in 6 cases, ear helix in 2 cases, ear helix and lobule in 2 cases, ear anti-helix in 2 cases, neck in 2 cases sternum in 2 cases, scapula in 2 cases and groin in 2 cases. Keloids ranged in size from 1 cm X 1 cm. to 8 cm X 10 cm. (Table 1) The keloids were excised using the Lumenis Carbon Dioxide (CO_2) laser (Lumenis, Palo Alto, CA, USA) with the 0.2 mm cutting handpiece, set at 100 millijoules/100 watts. Immediately after excision, 5cc of XoGlo (5Billion Exosomes) was injected into the wound base, and 1 cm around the perimeter in 0.2 cc aliquots, 1 cm. apart. If there was exposed cartilage, or if the excised wound bed had an area of 2.5cm2 or greater, a Human Amniotic Membrane Extracellular Matrix Graft (CTM Inc, Indianapolis, IN, USA) was employed for wound bed coverage. Patients were followed by the treating Physician daily for 10 days, weekly for 8 weeks and monthly for 2 years. For the first 3 weeks, an additional 3 Billion Exosomes (1.0 cc XoGlo Pro Kimera labs,; Miami, FL), was injected into the wound base and 1 cm around the perimeter of the wound. Kenalog 40, 1.0cc/ sq 2.2 cm was injected if any hypertrophic tissue was detected. Photographs were taken daily for the first 10 days, weekly for 1 month and monthly for 2 years.

Patient	Age	Sex	Race	Location	Size	Reoccurrence	Time
1	57	M	AA	Lobule	2x3	N	2 yrs
2	32	M	A	Helix	2x2	N	2 yrs
3	24	F	AA	Sternum	10x2	Y	8 wks
4	23	F	AA	Helix	3x2	N	2 yrs
5	40	F	AA	Groin	3x3	N	2 yrs
6	37	M	M	Lobule/Helix	4x4	N	2 yrs
7	29	M	I	Antihelix	3x3	N	2 yrs
8	38	F	C	Lobule	4x3	N	2 yrs
9	28	M	AA	Face	3x2	Y	6 wks
10	31	F	A	Scapula	6x5	N	2 yrs
11	29	F	AA	Groin	4x2	N	2 yrs
12	35	F	AA	Lobule	1x1	N	2 yrs
13	34	F	AA	Neck	5x3	N	2 yrs
14	43	F	M	Antihelix	2x2	N	2 yrs
15	53	M	AA	Neck	5x3	Y	4 wks
16	44	M	AA	Scapula	10x8	N	2 yrs
17	37	F	I	Lobule	3x4	N	2 yrs
18	42	M	AA	Sternum	8x2	N	2 yrs
19	50	M	C	Lobule	2x2	N	2 yrs
20	24	F	AA	Lobule/Helix	4x3	N	2 yrs
21	26	M	AA	Lobule	2x1	N	2 yrs

AA = African American C = Caucasian A= Asian I = Indian M = Mediterranean

Table 1: Patient Demographics.

Results

Over the 2 years of follow-up 18 of 21 patients with keloid scars developed no recurrence. Three patients of twenty-one developed a recurrence of their keloid scars within 2 months. Patient 3, a 24-year-old African American Female, developed a recurrence of a sternal keloid 8 weeks after excision. Patient 9, a 28-year-old African American Male, developed a recurrence on the right facial bearded cheek, 6 weeks after excision. Patient 15, a 53-year-old African American Male, developed a recurrence on his posterior-superior central hair-bearing neck 4 weeks after excision. When the recurrent keloids in patients 3, 9 and 15 were removed and concurrent laser hair modification (Lumenis 810nm. Diode Laser), was performed weekly for six weeks, all three recurrent keloids remained recurrence free after six months. All patients who were Fitzpatrick skin type 3-6 developed post-inflammatory hyperpigmentation in the areas of excision.

Discussion

Our skin has many functions. It is responsible for barrier maintenance between our internal and external environment. Skin is injured more frequently than any other organ. While the resulting damage is repairable, it leads to permanent scarring in mammals [15]. Over 100 million people worldwide, develop scars after trauma, surgery, burns, piercings, tattoos, vaccinations, and herpetic infections [16]. The end results include: a pencil-thin line, atrophic scars, hypertrophic scars, keloids, and non-healing wound beds [17,18]. Burn wounds unto themselves cause fibrotic scars creating billions of dollars of healthcare costs annually [19]. Functional problems such as contractures and symptoms such as pain and pruritis can adversely affect quality of life, physical status, and psychological health. The residual negative psychological effects of visible scars, particularly lowering one's sense of self-esteem can lead to body dysmorphism, and suicide in some cases [16]. Considerable progress has been made toward understanding the complex processes and pathways that regulate human wound healing. Knowledge of the molecular and cellular events during mammalian tissue repair is extensive [1,20-22]. Wound repair in fetal mammals has provided insight into molecular and cellular mechanisms of scar-free healing [7-11,23].

Urodeles possess the extraordinary ability to regenerate their limbs, spinal cords, hearts, internal organs, joints, and tails [24]. Adult axolotl salamanders (Ambystoma mexicanum) also possess the ability of healing skin in a "scar-free" manner [25]. Comparing scar-free healing in axolotls to scar formation in mammals revealed mammals to have an increased hemostatic response, slower re-epithelialization, increased early inflammatory response, increased and prolonged deposition of Extracellular Matrix (ECM), and a tripling in the time required for complete skin regeneration [25]. The author hypothesized that if the above wound healing processes could be duplicated in the human, perhaps a reversion to normal healing and possibly scar-free healing could be achieved. The goals of wound modulation would be to decrease inflammation, shorten hemostasis, and accelerate re-epithelialization and ECM deposition. It was determined that examining this potential by employing exosomes in keloid therapy was a reasonable model.

Keloid scarring continues to be a problem affecting millions of patients worldwide per year. There is a preponderance in the African American, Asian, Mediterranean, and Indian populations. An increasing number of younger and older patients are presenting for consultation in aesthetic offices with keloid scars. Many of these patients have had numerous attempts at removal of their keloids, most, with 100% recurrence. The majority of these had prior excision with cold steel (scalpel alone). The evolution of the surgical carbon dioxide (CO_2) laser (Coherent Lasers, PaloAlto, CA USA) in 1992, and associated cutting handpieces, led surgeons to begin excising keloids with this technology. Advantages included: blood free excision yielding meticulous delineation between scar tissue and healthy tissue, reduced pain due to the sealing off nerve endings, and a reduction of keloid recurrence, likely due to the anti-fibrotic nature of heat down-regulating fibroblasts. However, recurrence of keloids with this technique, was still in the 25% range. This trend has fueled the current explosion in expanding the knowledge and study of human placental mesenchymal stem cell-derived extra-cellular vesicles or exosomes in treating these scars.

The fields of cellular medicine, regenerative and stem cell therapy continue to grow exponentially. However, even with the extensive knowledge of the molecular and cellular processes involved in tissue repair, regenerative medicine pundits have yet to develop treatments that can regenerate mammalian skin without scarring. It is hypothesized that the regenerative effects of exosomes via growth factors, especially TGFbeta 3, IL-10, IL-12, MMP-2, MMP-9 and TNF-alpha, play a vital role in regulating "normal" wound healing and a "scarless" model, decreasing inflammation (TGFbeta-3), accelerating hemostasis and renewing vascularity (VEGF), accelerating re-epithelialization (TGFbeta-3, EGF, Amniotic membrane grafts) and accelerating ECM deposition and tissue regeneration (IL10, GDF15). Exosomes (extracellular vesicles) measure 50 -150 nm and are lipid membrane packets formed by a two-step budding process. First formed by inward budding of membranous vesicles in a multivesicular body, they fuse with the plasma membrane to release exosomes. Microvesicles are larger packets formed by direct budding of the plasma membrane. Both contain transmembrane proteins from their parent cells which aid in regulating uptake by other cells [17]. Exosomes contain messenger RNA (mRNA), microRNA (miRNA), and a multitude of proteins consisting of growth factors (Table 2) and immune factors. When properly stimulated, they illicit homing, regenerative, anti-inflammatory, immunomodulatory and anti-prostaglandin mechanisms.

BMP5	Stimulates Bone Growth
GDF15	Regulates inflammation, apoptosis, cell repair, and growth
OPG	Stimulates Bone Growth/Blocks Osteoclast Precursor Formation
G-CSF	Stimulates Bone Marrow to Procedure Granulocytes and Stem Cells
SCF	Responsible for Stem Cell and Melanocyte Growth
TGFß3	Most Important Anti-Inflammatory Protein. Converts Inflammatory T Cells into Anti-Inflammatory Regulatory T Cells.
VEGF	Stimulates Formation of Blood Vessels
ICAM-1	Binds Inflammatory Ligands on White Cells
IL-1RA	Binds and Sequesters the Inflammatory Cytokine IL-1
IL-6	Responsible for Macrophage Activation
IL-10	Anti-Inflammatory Cytokine responsible for Immunomodulation and Regulatory T Cell Conversion
MCP-1	Recruits Mononuclear Cells to Treatment Area
MIP-1	Also known as CC1-4, Recruits Mononuclear Cells to the Treatment Area
PDGF-BB	Growth Factor Used to Stimulate Healing in Soft and Hard Tissues
TIMP1 & TIMP2	Blocks Cartilage and Extracellular Matrix Degradation, Important for Cartilage Repair
HGF	Involved in Organ Regeneration and Wound Healing
GDNF	Promotes Survival of Neurons
BDNF	Supports Survival of Neurons and Encourage Growth
FGF	Potent Growth Factors Affecting Many Cells
TNFR1	Binds and Inactivates the Inflammatory cytokine TNF-*a*

Table 2: Key Growth Factors Present in MSC Exosomes.

Extracellular vesicles travel systemically without the risk of clumping. They do not demonstrate a first-pass effect into the lungs when administered intravenously as is commonly seen with MSC's. EV's can cross the blood-brain barrier without using mannitol [26]. Exosomes can evade the immune response as they contain no DNA, yielding no risk for malignant transformation. Mesenchymal Stem Cell Exosomes, (MSC exosomes) are produced by stem cells of connective tissue lineage which is the origin of skin, hair, bone, muscle, and cartilage. MSC exosomes are different from adult bone marrow exosomes which has a preponderance of hematopoietic stem cell exosomes. Another source of exosomes is derived from amniotic fluid. These are composed of primarily maternal epithelial cell exosomes. It is hypothesized that the ability of MSC exosomes to induce the synthesis of connective tissue is the basis for remarkable clinical benefits resulting from stem cell therapy [26]. The advantage of fetal MSC exosomes over exosomes from aged autologous or allogenic progenitor cells resides in the fact that with age, the number and function of MSC's in our tissue declines.

Aged autologous progenitor cells also produce less than 40% of the cytokines and differing miRNA's than perinatal MSC's. This secretome advantage of younger exosomes is therefore significant. After 2 years of follow-up, 18 of 21 patients treated with exosomes, remained free of recurrence (Table 1). All had previous excision of the same keloid with recurrence within a range of 2-6 months. These are promising results for the continuation of this Study over the next several years to examine further trends as new patients are entered into the Study and treated. All races were represented in the free of recurrence group. There were 8 males and 10 females. Ages ranged from 24 to 51. Success was achieved anatomically in all areas represented in the Study (Ear, Face, Neck Sternum, Scapula, Groin). Only 3 of 21 treated patients developed a recurrence of their keloid. All 3 were African American. This mirrors the demographic of African American Patients comprising a large majority of patients seeking treatment for keloids compared to other races. Factors leading to African Americans having a propensity for keloid scarring may also contribute to their increased propensity for recurrence post intervention.

Of the recurrences, there were 2 males and one female. As the population of males and females were relatively equal, no inference can be made in this Study as to sexual prediction for keloid production or recurrence. The female (Patient 3) was a 23-year-old African American. She developed a sternal recurrence at 8 weeks post excision. The second recurrence (Patient 9) was

a 28- year-old male who developed a right facial cheek recurrence 6 weeks after excision. The third, (Patient 16), a 53-year-old male, developed a posterior neck recurrence 4 weeks after excision. Common to all patients were recurrences in hair bearing regions that were not static, but actively moving. Review of treatment photos revealed the presence of hair at the base of the excised keloid with residual follicles in the wound bed. All patients with recurrences reported the propensity for folliculitis. It was hypothesized that the hair follicles were acting as a nidus for ongoing inflammation, stimulating recurrence of the keloid. It was decided with these patients to repeat the excision and immediately start treating the wound bed with a laser hair removal system. (Lumenis LightSheer, Lumenis Palo Alto, CA). After re-excision with this protocol, all 3 remain recurrence-free after 6 months. This supports the hypothesis that a prolonged inflammatory milleu increases the likelihood of abnormal scar formation. It is hypothesized that the propensity for recurrence on static areas such as an auricular helix, is less than that seen in moving areas such as the facial cheek, neck, or scapula. Non-recurrences were also observed long-term in mobile and stationary body locations. These were in non-hair-bearing areas. Intuitively, one would speculate, that a stationary wound has a better chance of healing without the sheering forces of a perpetually moving area. It appears that hair bearing, mobile parts of the body have a higher propensity for keloid formation and recurrence. This merits further, and expanded study (Figures 2-8).

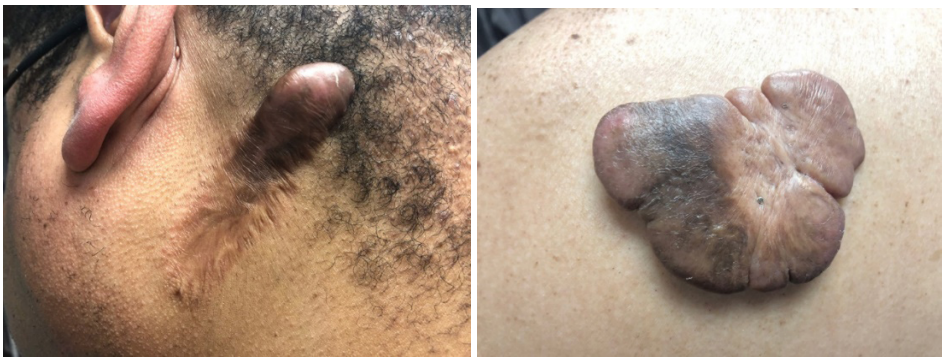

Figure 2: Left Posterior Neck Keloid- Patient 15; Left Scapular Keloid - Patient 16.

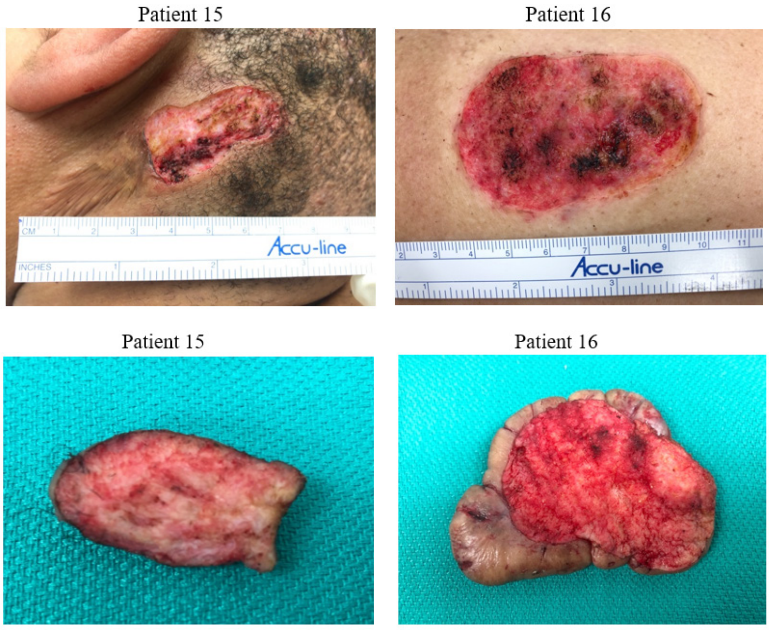

Figure 3: Excised wound beds, post CO_2 laser excision.

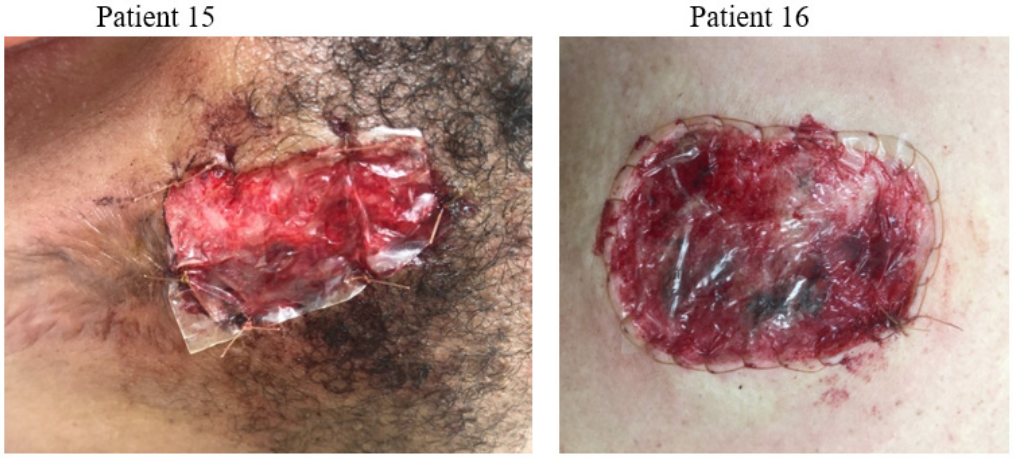

Figure 4: Keloid Excision, exosomes applied, amniotic membrane graft applied.

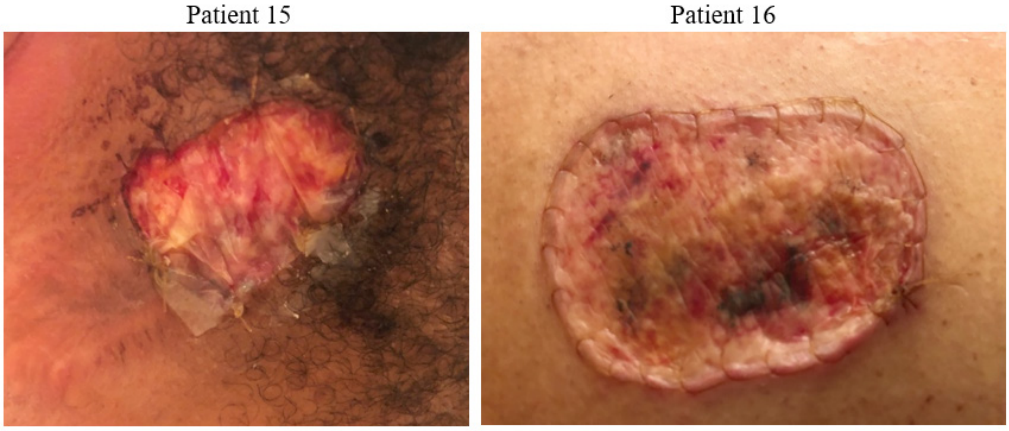

Figure 5: One week post excision.

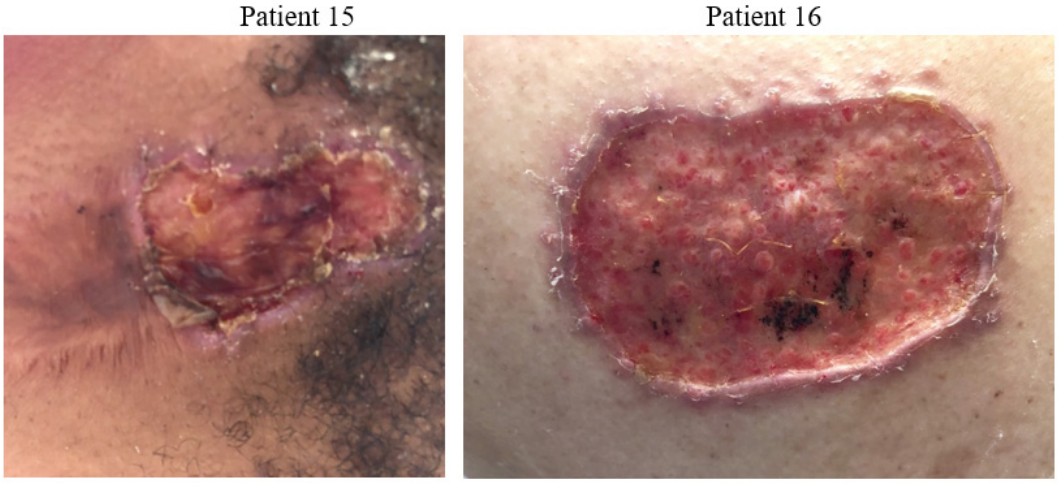

Figure 6: One month post excision.

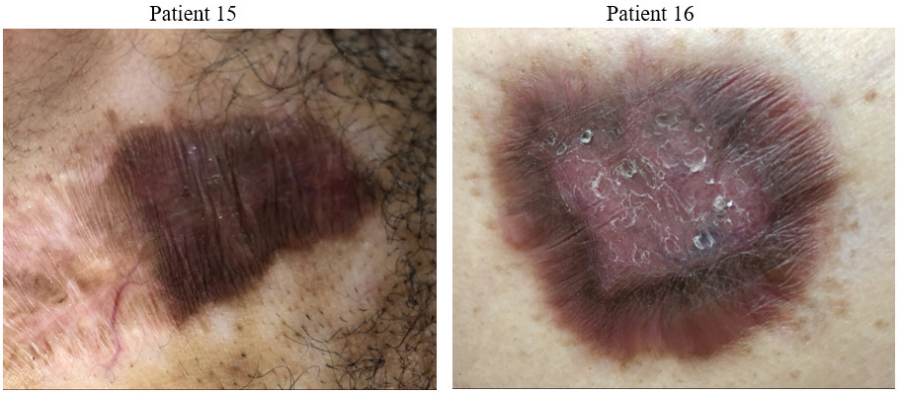

Figure 7: Post Excision: 2 years no recurrence.

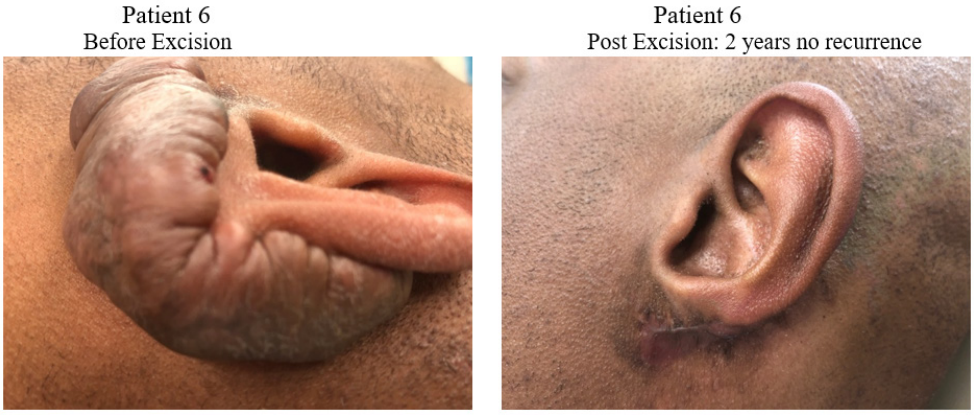

Figure 8: Before and After excision.

Exosome research is a rapidly progressing field. New methods are continuously being developed to facilitate the translation of exosome research to clinical applications. Exosome contents via liquid biopsies (blood, saliva, urine) can be evaluated for the potential of disease biomarkers [27]. This technology will shed further light on the propensity of keloids to occur in certain demographic groups such as race, age, and body location. The next limb of this Study will examine the exosome loads of non-keloid patients versus keloid patients, and recurrence patients versus non-recurrence patients. This will further the understanding of this complex problem.

Conclusion

This pilot study shows promising results in reducing the recurrence of keloid scars by combining initial excision with the carbon dioxide laser, immediate flooding of the excision bed and surrounding area with human placental fetal mesenchymal stem cell derived exosomes, tissue coverage with amniotic membrane grafts, and close follow-up with additional exosome applications if early fibrosis is detected. The pathophysiology remains extremely complex. Further Institutional Review Board (IRB) Approved Studies examining the diagnostic capabilities of exosomes secreted by keloid and hypertrophic scar patients to analyze their cytokine deficiencies and/or extremes will further streamline this exciting new alternative to a common problem.

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