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# Laser-Assisted Exosome Delivery (LAED) with Fractional $CO_2$ Laser: A Pilot Two-Case Report and Narrative Review

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## Abstract

Laser-assisted exosome delivery (LAED) combines ablative fractional lasers with immediate topical application of exosomes. Here, we introduce the LAED concept and report two uncontrolled feasibility observations: a 62-year-old man with atrophic acne scars and a 68-year-old woman with diffuse dyschromia underwent fractional $CO_2$ laser treatment followed by topical exosomes. Both cases showed early, encouraging signals of clinical improvement and shorter downtime, with good tolerability. An exploratory day-7 patient self-evaluation using a 5-point Likert scale for speed/comfort of recovery yielded 5/5 in both cases. Given the two-case, non-comparative design, causality cannot be inferred, and efficacy remains hypothesis-generating. These preliminary findings motivate controlled trials with standardized objective and patient-reported measures and longer follow-up to determine whether LAED truly enhances the cosmetic benefits of fractional laser treatment.

**Keywords:** laser-assisted exosome delivery (LAED); exosomes; fractional $CO_2$ laser; laser-assisted drug delivery (LADD); regenerative dermatology; aesthetic medicine; skin rejuvenation



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## 1. Introduction

Fractional ablative lasers are an established standard in esthetic and regenerative dermatology for the treatment of scars and skin rejuvenation [1,2]. Their ability to induce controlled dermal regeneration has expanded the therapeutic options for scars and skin aging, improving clinical efficacy and safety compared to traditional methods [3,4]. Among these technologies, the fractional $CO_2$ laser stands out for its versatility and effectiveness in a wide range of indications beyond rejuvenation, including the treatment of atrophic acne scars, hypertrophic scars, rhinophyma, striae distensae, surgical scars and photoaging damage [5–10]. Its ability to create microthermal ablation zones surrounded by healthy tissue promotes rapid re-epithelialization and prolonged dermal remodeling through the stimulation of neocollagenesis and elastin production [11–13]. However, the outcomes are not always optimal, and limitations persist, such as prolonged healing times and the

risk of adverse effects (erythema, post-inflammatory dyschromia) [14–17]. At the same time, new 'cell-free' therapies based on exosomes, small extracellular vesicles (40–160 nm), have emerged in recent years. Exosomes mediate intercellular communication by transporting proteins, nucleic acids and other bioactive factors [18,19]. Numerous studies have demonstrated their safety and efficacy in the medical field, stimulating a growing interest in dermatological regenerative applications [20,21]. Recent evidence suggests the potential of exosomes to promote skin rejuvenation, wound healing and the maintenance of healthy skin [22–24].

In this context, the integration of laser technologies with exosome-based therapies constitutes an innovative frontier. Several preclinical studies and initial clinical reports indicate that exosomes, whether applied topically or via minimally invasive methods, can amplify the regenerative outcomes of different dermatological procedures. Their content of growth factors, cytokines, and microRNAs is believed to enhance collagen production, regulate inflammation, and support more effective tissue remodeling [25–28].

Exosomes have been investigated not only in association with laser treatments but also combined with microneedling or as stand-alone therapy, underscoring their versatility as agents for esthetic skin regeneration [29–32].

Numerous recent publications have highlighted how exosomes can help overcome some of the limitations of laser treatments by modulating inflammation, promoting neocollagenesis and accelerating the restoration of the epidermal barrier. This combined action could be decisive in optimizing healing pathways and reducing the incidence of esthetic complications, especially in patients with skin at risk of hyperpigmentation or in protocols involving large skin areas [33–36]. The added value of exosomes lies in their ability to influence the dermal microenvironment at different levels: stimulation of fibroblasts and keratinocytes, modulation of melanocyte activity and control of local immune responses [37,38].

Furthermore, exosomes are also the subject of growing interest in other dermatological fields.

In the treatment of androgenetic alopecia, for example, clinical and preclinical studies have documented an increase in hair density and quality thanks to the use of mesenchymal cell-derived exosomes, suggesting a role in stimulating the dermal papilla and extending the anagen phase [39,40].

Similarly, in melasma, exosomes have been associated with a modulating effect on chronic inflammation and melanocyte activity, opening prospects for combined protocols with minimally invasive physical techniques [41,42].

These observations reinforce the rationale for exploring LAED as an integrated approach that combines physical stimulation and biological support to enhance skin regeneration. Fractional $CO_2$ laser, thanks to its ability to induce controlled microdamage and its established efficacy profile in the treatment of scars, striae distensae, rhynophima, and photoaging, represents the ideal platform for the application of synergistic strategies with exosomes [5–10]. In this context, the goal is to maximize clinical benefits while minimizing recovery times and side effects, with a view to increasingly personalized regenerative medicine.

In this article, we aim to provide a comprehensive review of the scientific rationale supporting the combination of fractional laser-induced microchannels and exosomes, highlighting the biological basis for this therapeutic synergy.

We will also provide a detailed overview of the main preclinical and clinical evidence demonstrating the possible role of exosomes in enhancing skin repair and remodeling processes. A specific section will be dedicated to the presentation of two original clinical cases illustrating the application of Laser-Assisted Exosome Delivery (LAED) for the treat-

ment of acne scars and photoaging-induced dyschromic pigmentation, with standardized photographic documentation.

Lastly, we will address possible protocol optimizations and future research directions to support large-scale controlled trials and promote the safe and effective integration of this technique into clinical practice.

## 2. Laser-Assisted Drug Delivery (LADD)

Laser-Assisted Drug Delivery (LADD) represents a technological advancement in the transcutaneous administration of therapeutic agents. This technique was developed to overcome the limitations associated with the low skin bioavailability of conventional topical drugs [43]. LADD employs the controlled ablative action of lasers to increase the permeability of the skin barrier, particularly the stratum corneum, thereby enhancing the penetration and diffusion of active molecules into deeper skin layers [44].

The most used lasers for this purpose are $CO_2$ and Er:YAG (Erbium-doped Yttrium Aluminum Garnet) in both conventional ablative and fractional modes. Their ability to generate vertical microchannels in a precise and reproducible manner makes them particularly suitable for LADD [45].

Preclinical and clinical studies have demonstrated that fractional ablative lasers significantly increase tissue drug concentration. A single pass of fractional $CO_2$ laser, for example, can create microchannels approximately 300 µm in diameter and 1.8 mm deep, allowing radial diffusion up to 1.5 mm from the channel margins [46].

Among its main dermatological applications, LADD enhances the penetration of corticosteroids for the treatment of hypertrophic and keloid scars [47–49].

It is also used for delivering photosensitizing agents in photodynamic therapy, as well as depigmenting and biostimulating agents for esthetic and regenerative purposes [50–52]. Recent studies have highlighted its potential in increasing the bioavailability of topical chemotherapeutics, such as 5-fluorouracil, for the treatment of precancerous lesions and superficial skin carcinomas [53]. This results in significantly improved intracutaneous absorption compared to conventional topical application.

LADD has also shown promise in local anesthesia. The use of fractional lasers to enhance the penetration of topical anesthetics, such as articaine with epinephrine, has enabled effective anesthesia within 10–15 min, with precise control of microchannel depth and density [54]. The success of these applications is linked to the ability of laser-created microchannels to bypass skin barriers and facilitate the transport of large or hydrophilic molecules.

There is growing interest in comparing LADD with other transcutaneous delivery techniques, such as microneedling and radiofrequency [55,56]. While these methods share the goal of overcoming the stratum corneum, LADD offers superior control over microchannel depth, density, thermal effect, and lesion geometry. This precision allows tailoring to the specific active agent and clinical indication, making LADD particularly suitable for temperature-sensitive molecules and for delicate or difficult-to-treat areas [57].

Despite significant progress, LADD still presents areas for development. Further work is needed to standardize protocols, define optimal parameters for different clinical indications, and select the most appropriate agents for laser-assisted delivery.

In this context, the integration of exosomes offers particularly innovative possibilities. Their nanometric size and rich bioactive content make exosomes ideal candidates for delivery via laser-induced microchannels. Combining physical laser stimulation with biological support from exosomes could define a new frontier in regenerative medicine and support the development of more effective and safer protocols.

Finally, one of the main limitations of LADD is the difficulty in accurately quantifying the amount of active ingredients absorbed into the skin. Absorption can also vary depending on skin type and anatomical location [58,59].

These challenges underscore the need for further experimental and clinical studies to optimize delivery strategies and ensure predictable, reproducible outcomes in daily practice.

## 3. Exosomes in Dermatology

Exosomes are small extracellular vesicles (40–160 nm in diameter) produced by almost all cell types and considered to be fundamental mediators of intercellular communication. By transporting proteins, lipids, mRNA, microRNA and other metabolites inside them, exosomes transfer biochemical signals between different cells, modulating their behavior. Due to their nanometric size, biocompatibility and ability to cross biological membranes, they show considerable therapeutic potential [60,61].

Exosomes have attracted increasing interest in dermatology due to their multifunctional role in skin homeostasis and disease modulation. These extracellular vesicles are naturally involved in maintaining tissue integrity, immune regulation, and cellular communication within the cutaneous microenvironment [62–64].

Recent preclinical and clinical studies have investigated the application of exosomes in a wide range of dermatological conditions, including chronic wounds, inflammatory and autoimmune skin diseases (such as psoriasis and atopic dermatitis), and superficial skin cancers. In these contexts, exosomes have demonstrated the ability to modulate angiogenesis, fibroblast activation and extracellular matrix remodeling, supporting faster and more balanced tissue repair. They can downregulate pro-inflammatory cytokines (e.g., TNF-α, IL-6), inhibit pathogenic T-cell activation, and restore the balance between effector and regulatory pathways [65–67].

Exosomes derived from mesenchymal stem cells (MSCs) have emerged as promising regenerative agents capable of reproducing many of the beneficial effects of stem cells without associated risks. They show strong anti-inflammatory, antioxidant and pro-regenerative properties. In animal models of wounding, MSC-derived exosomes accelerated healing and reduced scar formation [68].

Moreover, exosomes from bovine colostrum, rich in growth factors, have been shown to protect skin cells from UV (ultraviolet) damage and reduce melanin production in UVB-irradiated melanocytes, contributing to the prevention of post-inflammatory hyperpigmentation [69].

Several recent studies have further documented the potential of exosomes as standalone treatments or in combination with other minimally invasive procedures.

For example, Proietti et al. reported encouraging results with the combination of microneedling and exosomes derived from Rosa damascena stem cells for melasma. This approach demonstrated significant reductions in pigmentation indices and improved skin homogeneity [41].

Similarly, Ersan et al. showed that the intradermal injection of foreskin-derived mesenchymal stromal cell exosomes significantly increased hair density in patients with androgenetic alopecia, with sustained patient satisfaction and no adverse effects [39].

These findings reinforce the versatility of exosomes as therapeutic agents not only in laser-assisted protocols but also as monotherapy or combined with microneedling.

In summary, thanks to their ability to regenerate tissue, modulate inflammation and regulate skin pigmentation, exosomes represent a new therapeutic frontier in esthetic and regenerative dermatology.

## 4. Integrated Methods and Clinical Evidence

In this pilot study, we combined state-of-the-art fractional $CO_2$ laser resurfacing with rigorously characterized bovine colostrum exosomes to explore the feasibility of laser-assisted exosome delivery (LAED) in two prototypical esthetic indications (Table 1). Exosome sera (Exolight C for collagen stimulation and Exolight M for depigmentation; DEKA M.E.L.A., Florence, Italy) were manufactured in an ISO 13485-compliant and CE-marked facility [70]. Vesicles were purified by sequential low-speed centrifugation, tangential flow filtration, and ultracentrifugation (120,000× *g*, 2 h). Nanoparticle tracking analysis (NanoSight NS300, Malvern Panalytical Ltd., Malvern, UK) showed a mean diameter of 110 ± 18 nm with $3.2 \times 10^{11}$ particles/mL$^{-1}$; >90% of the particles expressed CD63/CD81 and were calnexin-negative by bead-based flow cytometry. Endotoxin content was <0.05 EU mL$^{-1}$ by LAL assay, and sterility was confirmed after 14-day aerobic/anaerobic culture. Aliquots were stored at −80 °C and thawed once immediately before use. This study was approved by the Local Ethics Committee of the Calabria Region (protocol code 374, 17 December 2019).

**Table 1.** Cases description.

| Case | Age/Sex | Indication | Laser—Mode and Parameters | Exosome Serum | Downtime * | Clinical Improvement | Patient Self-Evaluation (Day 7) ‡ | Adverse Events |
|---|---|---|---|---|---|---|---|---|
| 1 | 62 M | Atrophic acne scars | Fractional $CO_2$, Smart-Pulse 14 W ⋯ dwell 800 µs ⋯ spacing 550 µm (2 sessions, 4 weeks apart) | Exolight C (pro-collagenic) | 5–6 days (erythema + edema) | Visible scar depth/texture less marked (clinician estimate) | 5/5 | None |
| 2 | 68 F | Photo-aging dyschromia | Fractional $CO_2$, CoolPeel 5 W ⋯ spacing 500 µm ⋯ High-Pulse (single session) | Exolight M (depigment-ing) | 2 days (mild erythema/micro-peel) | UV pigment score less ~30% at 4 weeks † | 5/5 | None |

* Time to social-downtime resolution (no concealing make-up). † Objective imaging (VISIA® UV or standard, Canfield Scientific, Parsippany, NJ, USA) at 4–8 weeks. ‡ Exploratory 5-point Likert scale for speed/comfort of recovery (1 = very slow/uncomfortable; 5 = unexpectedly fast/comfortable); non-validated, used only for feasibility/tolerability.

Both patients were treated with the SmartXide Tetra PRO fractional $CO_2$ platform and the DOT PRO scanner (DEKA M.E.L.A.). For atrophic acne scars (62-year-old man), standard resurfacing parameters were 14 W, 800 µs dwell time, and 550 µm spacing in Smart-Pulse mode; two sessions were performed four weeks apart. For diffuse photoaging-related discoloration (68-year-old woman), a single CoolPeel pass (5 W, 500 µm spacing, High-Pulse mode) provided gentle fractional ablation. Immediately after laser irradiation, the skin was cleansed with sterile saline, then 2 mL of the relevant exosomal serum was massaged into the treated area for two minutes and left under hydrocolloid occlusion for 20 min. Residual serum was not removed to maximize transepidermal absorption.

Post-procedure care was consistent: Vaseline twice daily for 48 h, followed by 5% panthenol cream until re-epithelialization and SPF 50+ sunscreen from day 3 onwards. Analgesia was limited to 1 g of paracetamol as needed.

Objective endpoints are being prospectively acquired. Acne scars are classified using the Échelle d'Évaluation Clinique des Cicatrices d'Acné (ECCA). Standardized photographs were obtained with the VISIA® (Canfield Scientific, Parsippany, NJ, USA) complexion analysis system. In cases of dyschromia, UV images were acquired to derive a UV pigmentation score, reported in Results and Table 1. High-frequency ultrasound (DermaScan C, 20 MHz, Cortex Technology, Aalborg, Denmark) and optical coherence tomography (VivoSight DX, Michelson Diagnostics Ltd., Maidstone, UK) were used to quantify epidermal thickness, collagen density, and vascularity at baseline and at weeks 4, 12, and 24.

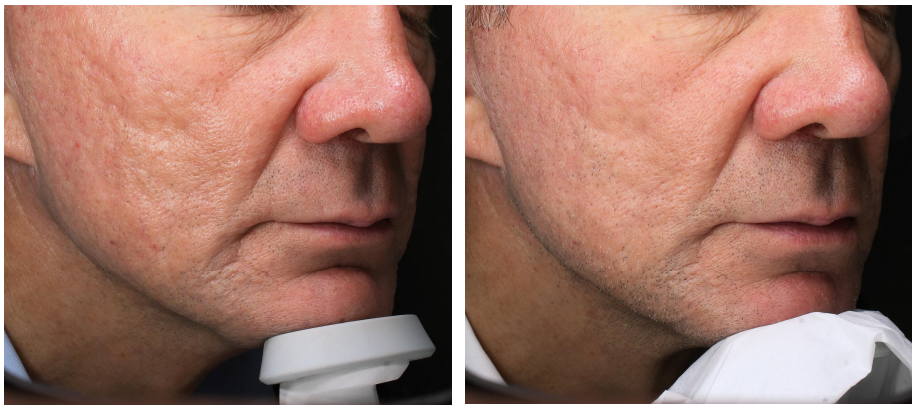
In addition to these objective endpoints, we administered a 5-point Likert scale for speed/comfort of recovery on day 7 after the procedure in both cases (reference points:

1 = very slow and uncomfortable; 2 = slow and slightly uncomfortable; 3 = moderate; 4 = rapid and somewhat comfortable; 5 = unexpectedly rapid and comfortable). This tool is not validated and is used solely for feasibility/tolerability purposes; validated FACE-Q modules were programmed as above. Future studies will standardize PROM selection, timing (including day 7 acquisition), minimal clinically relevant difference, and analysis.

In summary, for acne scars, post-laser erythema and edema resolved in 5–6 days, faster than the 8–12 days typically reported for comparable $CO_2$ settings, and VISIA® photography at week 8 documented significant smoothing of box-shaped and wavy depressions without post-inflammatory hyperpigmentation. For dyschromia, downtime was limited to two days of mild erythema and microexfoliation; by week 4, analysis in UV mode indicated an approximately 30% reduction in UV pigmentation score with a visibly brighter and more even texture. No adverse events occurred in any of the patients.

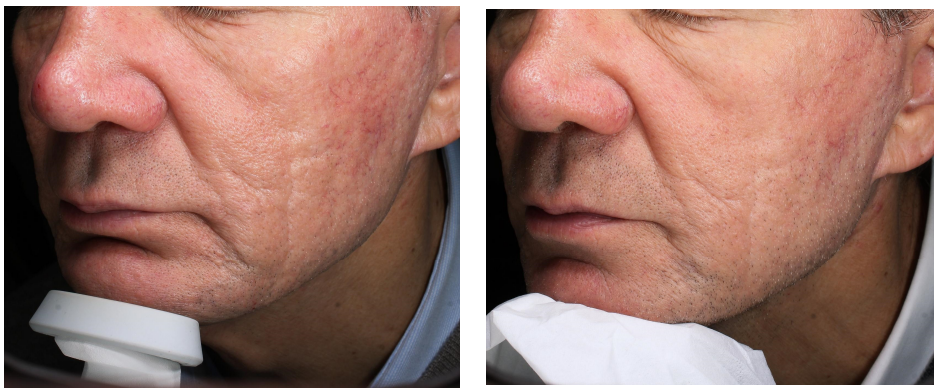
### *4.1. Case 1—Atrophic Acne Scars*

A 62-year-old male patient presented with multiple atrophic acne scars on his face, mainly located on the cheeks (Figures 1 and 2). A LAED protocol was proposed to take advantage of the greater efficacy of fractional ablative $CO_2$ combined with the regenerative effect of exosomes. The treatment consisted of two sessions, four weeks apart. In each session, after application of topical anesthetic cream, an ablative fractional $CO_2$ laser treatment (SmartXide Tetra PRO, DEKA M.E.L.A Srl, Florence, Italy), equipped with a dedicated scanner system (DOT PRO scanner, DEKA M.E.L.A, Florence, Italy) was performed on the entire face. The parameters used were as follows: power 14 W, dwell time 800 µs, spacing 550 µm, Smart Pulse mode. Immediately after the laser treatment, the area was cleansed with saline solution and then covered with Exolight C.



(**a**) (**b**)

**Figure 1.** (**a**) Right side of the face before treatment and (**b**) four weeks after the last LAED session.



(**a**) (**b**)

**Figure 2.** (**a**) Left side of the face before treatment and (**b**) four weeks after the last LAED session.

At day 7, the patient rated the speed and comfort of recovery with a score of 5/5 on a 5-point Likert scale. Clinically post-laser erythema and edema resolved within 5–6 days (compared to 8–12 days typical for fractional $CO_2$ at those settings), with minimal desquamation.

After the second session, at 8 weeks, clinical evaluation showed a marked reduction in the depth and visibility of acne scars, with improvement in the surrounding skin texture (Figures 1 and 2). Pre- and post-treatment comparison photos confirmed a clear smoothing of the scars. The patient tolerated the procedures well, with no infections or post-inflammatory hyperpigmentation (PIH). Patient-reported recovery was favorable; even if Future studies should incorporate validated PROMs, e.g., FACE-Q, and blinded grading. In summary, the addition of exosomes may have contributed to improved clinical outcomes and appeared to shorten healing times.

### *4.2. Case 2—Diffuse Hyperpigmentation of the Face*

A 68-year-old female patient presented with diffuse hyperchromic spots on her face (senile lentigines and photoaging-induced dyschromic pigmentation), associated with uneven skin texture and fine roughness (Figure 3).

(**a**) (**b**)

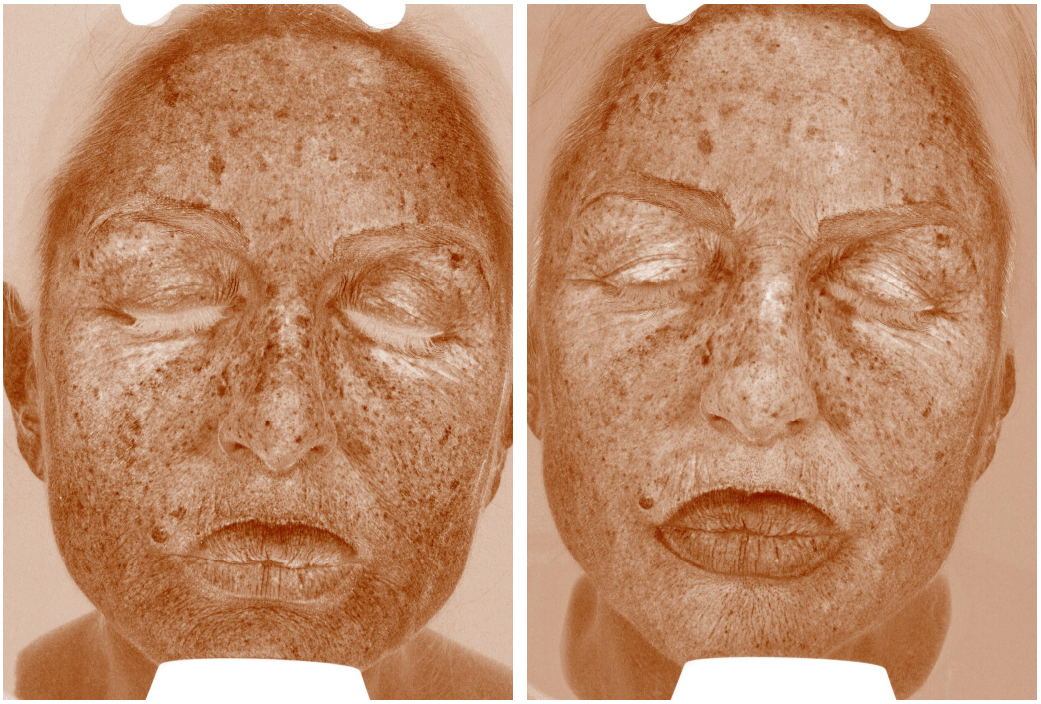
**Figure 3.** (**a**) Frontal clinical image before treatment and (**b**) four weeks after the LAED session.

A single treatment was chosen with ablative fractional $CO_2$ laser (SmartXide Tetra PRO, DEKA M.E.L.A Srl, Florence, Italy) and topical exosomes with depigmenting activity (Exolight M).

In particular, the CoolPeel mode (DEKA M.E.L.A Srl, Florence, Italy) of the $CO_2$ laser was used to perform light resurfacing focused on the hyperpigmented areas, while minimizing downtime (power 5 W, spacing 500 µm, High pulse mode). Immediately after the laser treatment, a layer of Exolight M was applied to the face.

The patient experienced only mild erythema and fine exfoliation in the following two days, allowing her to resume normal social activities with no erythema, as early as the third day after treatment (downtime significantly lower than her previous experiences with fractional lasers).

Four weeks after the session, clinical and instrumental examination showed an overall reduction in hyperpigmentation of approximately 30% compared to the baseline (Figure 3). Digital analysis using UV photography confirmed the decrease in pigment index in the treated areas (Figure 4).



(**a**) (**b**)

**Figure 4.** (**a**) Pre-treatment UV imaging acquired via the VISIA® system and (**b**) four weeks after the LAED session.

The patient reported a subjective improvement in skin brightness and evenness, consistent with the attending physician's clinical assessment and confirmed by comparative photographic documentation. At day 7, the patient rated the speed and comfort of recovery as 5/5 on the 5-point Likert scale. While these observations are encouraging, they are based on non-standardized assessments. Future studies should integrate validated PROMs, such as the FACE-Q, along with objective assessment tools to provide reproducible and comparable evidence. No complications were observed in this case.

## 5. Laser-Assisted Exosome Delivery (LAED)

Laser-Assisted Exosome Delivery (LAED) is a new therapeutic approach that delivers exosomes through laser-generated microchannels in the stratum corneum.

This method is based on the same principles as Laser-Assisted Drug Delivery (LADD), previously discussed, exploiting the formation of microablative zones (MAZs) in the stratum corneum to facilitate the penetration of active molecules into deep skin tissues. The use of fractional $CO_2$ lasers allows the creation of epidermal and dermal microchannels through which exosomes can be more effectively assimilated by fibroblasts, keratinocytes and melanocytes. Thanks to their bioactive properties, exosomes contribute to modulating the post-procedural inflammatory response, stimulate regenerative processes and improve the overall safety profile, reducing recovery times.

The two clinical cases presented in this study offer preliminary clinical observations consistent with potential benefits of LAED. In both patients, topical application of exosomes immediately after fractional $CO_2$ treatment appeared to result in faster and more marked

improvement than typically expected based on laser use alone; however, these signals are hypothesis-generating and non-confirmatory.

Recent studies have further explored the integration of exosomes with laser technologies.

A significant contribution to the clinical validation of LAED comes from the randomized, double-blind, split-face study conducted by Kwon et al. on 25 patients with atrophic acne scars. Patients were treated with three sessions of fractional $CO_2$ laser on the entire face, immediately followed by the application of a gel containing adipose stem cell-derived exosomes (ASCE) or a placebo gel on each half. Efficacy was assessed using the ECCA (Échelle d'Évaluation Clinique des Cicatrices d'Acné) score and standardized imaging assessment at 12 weeks. The side treated with exosomes showed a significantly greater reduction in total ECCA score than the control side (32.5% vs. 19.9%; $p < 0.01$), with superior results also for the icepick, boxcar and rolling acne scar subtypes. In addition, patients reported a shorter subjective recovery time (mean 4.1 days vs. 4.3; $p = 0.03$) and less post-treatment erythema. These data confirm the clinical efficacy of the combination of fractional $CO_2$ and exosomes in improving not only the quality of dermal regeneration but also the tolerability of the treatment [71].

Further interesting evidence is provided by the preclinical study conducted by Fusco et al., which evaluated the efficacy of bovine-derived Exolight exosomes as adjuvants to fractional $CO_2$ laser treatment. This study included both in vitro analyses and in vivo preclinical models, documenting anti-melanogenic, pro-collagenic and anti-inflammatory activity. In particular, combined use with $CO_2$ laser showed a significant reduction in post-treatment healing time, associated with faster crust detachment and less residual vascularization in the first few days after the procedure, as evidenced by high-resolution OCT imaging. The 3D and cross-sectional images obtained with Optical Coherence Tomography (OCT) have documented a faster resolution of erythema and early normalization of the vascular network, confirming the anti-inflammatory effect of exosomes in the context of post-laser inflammation [72]. These results highlight how Laser-Assisted Exosome Delivery (LAED) can not only enhance clinical efficacy but also reduce healing time, improving patient quality of life. Faster recovery allows for a quicker return to daily and social activities—an increasingly relevant factor in a society where visual appearance, especially on social media, plays a major role. This is particularly significant among younger individuals, who use platforms like Instagram and TikTok as primary sources of skin health content [73].

Lueangarun et al. described a clinical case of pilary repigmentation in a patient with androgenetic alopecia with circumscribed poliosis. The subject was treated with fractional 1064 nm Nd:YAG (Neodymium-doped Yttrium Aluminum Garnet) picosecond laser combined with topical application of exosomes. The protocol led to a clear improvement in both hair density and pigmentation of the depigmented hair tuft, with excellent tolerability and no significant side effects. These data suggest a dual effect of exosomes in the trichological field, acting both on follicular regeneration and on the modulation of the epithelial pigmentary unit, thanks to paracrine communication mediated by miRNAs contained in the exosomes themselves [40].

Finally, Mirzadeh et al. presented a series of cases in which patients with androgenetic alopecia, unresponsive to conventional treatments (platelet-rich plasma, minoxidil, mesotherapy), were treated with a combination of Low-Level Laser Therapy (LLLT) and autologous exosomes obtained from adipose MSCs. The clinical results, observed after two sessions, documented an improvement in hair density and thickness, with a synergistic effect attributed to the interaction between laser stimulation and the regenerative potential of exosomes. The effect was also attributed to the modulation of intracellular pathways such as Transforming Growth Factor-beta (TGF-β), Nuclear Factor kappa-B (NF-κB) and/or

Hypoxia-Inducible Factor-1 (HIF-1) and to the increase in mitochondrial ATP production induced by laser [74].

These initial observations suggest the strong biological rationale and clinical potential of LAED and open broader application scenarios. The synergistic combination of laser and exosomes could be used in various dermatological indications. For example, in the treatment of striae distensae, the addition of pro-collagenic exosomes could improve the quality of dermal regeneration.

Another potential application is the management of skin discoloration using fractional picosecond lasers combined with depigmenting exosomes.

Furthermore, it remains an area of active investigation whether exosomes could be effectively combined with other laser sources or light-based devices, such as dye lasers or intense pulsed light systems, to expand therapeutic possibilities [75].

LAED also raises open questions. The regulation of exosomes, currently situated in a regulatory gray zone between cosmetic products, biological agents and medical devices, will require clearer legal definitions depending on their origin, processing, and intended use. Critical aspects such as standardization of production, sterilization and storage must be strictly controlled [76].

## 6. Limitations

We acknowledge that this work represents an exploratory proof-of-concept rather than a definitive clinical study, and several factors limit the robustness of our conclusions.

The evidence comes from only two uncontrolled cases, which, while useful for illustrating feasibility and providing preliminary clinical documentation, do not allow us to quantify the true effect size or separate the potential contribution of exosomes from the natural course of wound healing.

Furthermore, outcomes were assessed primarily through clinical photographs, physician judgment, and patient satisfaction. While these approaches reflect daily practice, they lack the rigor of blinded assessment and standardized outcome measures. Future studies should therefore include validated.

Patient-reported questionnaires, such as the FACE-Q, along with objective quantifications such as the ECCA score, Mexameter indices, or advanced imaging methods (OCT, high-frequency ultrasound) to ensure reproducibility and comparability. Another limitation is the short follow-up, limited to 4–8 weeks, which is sufficient to document early re-epithelialization but not long-term pigment stability, collagen remodeling, or delayed adverse events. Further observation will be needed to establish both durability and safety. Although quality control parameters for exosome preparations have been reported, important aspects such as batch-to-batch consistency, post-thaw stability, and dose–response relationships have not been studied, limiting reproducibility between centers. Finally, both patients were older adults with lighter skin types, and the results cannot be generalized to other age groups, skin types, or comorbid conditions.

Overall, these limitations indicate that this report should be interpreted only as a preliminary feasibility study, primarily documenting the tolerability of combining fractional $CO_2$ laser with topical exosomes. The hypothesis that LAED can improve clinical outcomes or reduce recovery times remains a hypothesis and cannot be confirmed based on this work. Moreover, the literature is currently limited; additional well-designed studies are needed. Explicitly acknowledging these limitations, our intention is to stimulate and guide the design of larger, controlled clinical trials with standardized outcome measures and longer follow-ups, which will be essential to establish whether LAED can evolve into a reliable, evidence-based therapeutic strategy in regenerative dermatology.

## 7. Future Perspectives and Conclusions

Laser-assisted exosome delivery (LAED) is a promising emerging approach in esthetic and regenerative dermatology, but current evidence remains preliminary. The two cases presented suggest that the combination of fractional $CO_2$ laser and topical exosomes is technically feasible and appears well-tolerated, with encouraging early signs of clinical improvement. However, these observations cannot establish efficacy and should be considered only as hypothesis-generating.

Before LAED can be considered a reliable and reproducible therapeutic strategy, several challenges must be addressed. Standardized protocols are needed to clarify the optimal parameters for each indication, including laser settings, exosome source and concentration, number and frequency of sessions, timing and method of application, and most importantly, the tools used to assess outcomes. Future studies should employ validated patient-reported questionnaires and objective quantitative measures to ensure reproducibility and comparability across centers. Long-term safety also requires systematic investigation to rule out late-onset adverse events and confirm the durability of results. Equally important is the standardization of exosome manufacturing, sterilization, storage, and quality control procedures, along with a clearer regulatory framework defining their classification and use in clinical practice. Advances in these areas will enable the design of well-controlled clinical trials on larger populations, capable of quantifying the true contribution of exosomes beyond conventional laser treatment and testing the underlying biological rationale with statistical validity.

Only through such a rigorous and collaborative scientific approach will it be possible to determine whether LAED can evolve from a proof-of-concept proposal to an evidence-based therapeutic option, supporting its safe and effective integration into modern dermatology. Until such evidence is available, LAED, while promising, should still be considered experimental.

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**Data Availability Statement:** The data supporting the findings of this study are available within the article.

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## Abbreviations

| | |
|---|---|
| ASCE | Adipose Stem Cell–derived Exosomes |
| ATP | Adenosine Triphosphate |
| $CO_2$ | Carbon Dioxide |
| ECCA | Échelle d'Évaluation Clinique des Cicatrices d'Acné |
| Er:YAG | Erbium-doped Yttrium Aluminum Garnet |
| EU | Endotoxin Unit(s) |
| FACE-Q | Facial Aesthetic Clinical Evaluation Questionnaire |

| | |
|---|---|
| HIF-1 | Hypoxia-Inducible Factor-1 |
| ISO | International Organization for Standardization |
| LADD | Laser-Assisted Drug Delivery |
| LAED | Laser-Assisted Exosome Delivery |
| LAL | Limulus Amebocyte Lysate (assay) |
| LLLT | Low-Level Laser Therapy |
| MAZ(s) | Microablative Zone(s) |
| MSC(s) | Mesenchymal Stem Cell(s) |
| Nd:YAG | Neodymium-doped Yttrium Aluminum Garnet |
| NF-κB | Nuclear Factor kappa-B |
| OCT | Optical Coherence Tomography |
| PIH | Post-Inflammatory Hyperpigmentation |
| PRP | Platelet-Rich Plasma |
| PRO(s) | Patient-Reported Outcome(s) |
| PROM(s) | Patient-Reported Outcome Measure(s) |
| SPF | Sun Protection Factor |
| TNF-α | Tumor Necrosis Factor-alpha |
| UV | Ultraviolet |
| UVB | Ultraviolet B |
| VISIA® | VISIA® Complexion Analysis System |

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