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Regenerative Aesthetic Medicine: The Future of Non-Injectable Cellular Therapy and Restoration of Dermal Homeostasis

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Abstract

The shift of contemporary aesthetic medicine toward non-invasive interventions necessitates not only clinical verification of their efficacy but also a profound understanding of the underlying mechanisms that extend far beyond trivial stimulation of collagen genesis. The aim of the study is the conceptual systematization of molecular determinants (epigenetic and mitochondrial) and the evaluation of the clinical effectiveness of synergistic non-injectable protocols focused on the restoration of dermal homeostasis. The methodological framework of the work is based on a systematic review of scientific literature devoted to the biophysical and cellular foundations of non-injectable therapeutic interventions, as well as on a retrospective analysis of a clinical case study of a multimodal protocol (N=40, DermaReboot Protocol). The obtained data indicate that non-injectable energy-based interventions, in particular photobiomodulation and microcurrent therapy, mediate modification of the cellular response predominantly through non-thermal pathways, including activation of mitochondrial ATP synthesis and key epigenetic regulators (SIRT1, FOXO). Synergistic regimens integrating device-based stimulation (RF, EMS, LED) with topical delivery of signaling molecules (peptides and growth factors) demonstrate objectively measurable clinical effectiveness: there is a statistically significant increase in skin elasticity (on average by +47%) and a pronounced reduction in wrinkle depth (on average by -42%). Rational, intelligent integration of biophysical stimuli and signaling molecules forms a validated and physiologically substantiated strategy of non-injectable dermal regeneration aimed at restoring the homeostatic balance of the skin. The presented work

has substantial scientific and practical significance for dermatology researchers and clinicians working in the field of regenerative and aesthetic medicine.

Keywords: regenerative aesthetics, non-injectable therapy, dermal homeostasis, epigenetic regulation, photobiomodulation, mitochondrial activation, intelligent delivery, exosomes, synergistic protocols, cellular therapy.

Introduction

Contemporary aesthetic medicine is undergoing a profound transformation, manifested in a stable shift of clinical and consumer interest toward non-invasive and non-injection therapeutic protocols. This shift is driven by a combination of sociocultural determinants, including the demand for natural rejuvenation without a pronounced rehabilitation period, and by increased visual self-reflection in the context of the dominance of digital communications (the so-called Zoom-face effect). This, in turn, leads to a growing preference for procedures with rapid, clinically noticeable and visually verifiable outcomes.

Forecast and statistical market data convincingly confirm this trend. The global medical aesthetics market, estimated at 89.64 billion US dollars in 2024, is projected to reach 239.98 billion US dollars by 2033, demonstrating a compound annual growth rate (CAGR) of 11.73% [1]. Within this macrotrend, the segment of non-invasive aesthetic procedures, estimated at 22.67 billion US dollars in 2025 [2], represents one of the key growth drivers.

A detailed analysis of market segmentation reveals an important feature of its dynamics: injection-based methods (neuromodulators and dermal fillers) maintain a leading share of about 35.2% [3] or, according to alternative estimates, 57.15% in 2024 [4]. However, it is the segment of non-invasive energy-based (device-based) technologies aimed at skin rejuvenation that demonstrates one of the highest projected growth rates (CAGR of about 11.31% through 2030) [4]. This indicates that the technological potential of device-based medicine is developing at an accelerated pace, seeking to satisfy the growing demand for therapeutic solutions with minimal invasiveness.

At the same time, the fundamental scientific justification of the efficacy of the corresponding methods lags significantly behind the breadth of their practical use. The research gap manifests itself in the predominantly limited nature of current studies, which, as a rule, consider individual modalities (for example, radiofrequency (RF) lifting alone or photobiomodulation (PBM) alone) and reduce the mechanism of action mainly to thermally dependent induction of neocollagenesis. Both the synergistic effects of combined protocols and their integral impact on basic cellular processes are less well studied, primarily with respect to epigenetic regulation, restoration of mitochondrial function, and maintenance of dermal homeostasis [19, 21].

Objective of the study: to systematize and critically analyze the molecular biological mechanisms (mitochondrial and epigenetic), as well as the clinical efficacy of modern non-injection approaches to dermal regeneration in the context of a synergistic multimodal protocol model.

The author's hypothesis is based on the premise that the combined use of non-injection physical (energy-based) stimuli and topical (signaling) agents initiates more durable and physiologically adapted dermal regeneration through profound epigenetic modulation and restoration of mitochondrial function, while the overall effect exceeds the simple additivity of each modality used in isolation.

The scientific novelty of the study is determined by the fact that non-injection methods are considered within the paradigm of an integrative biophysical system capable of modulating dermal homeostasis at the epigenetic level (the SIRT1/FOXO axis) and at the level of mitochondrial metabolism (ATP synthesis), rather than as a set of isolated physiotherapeutic interventions described predominantly in terms of a local tissue response.

Materials and Methods

The methodological foundation of the study is integrative in nature and is based on a combination of a systematized analysis of scientific literature with the retrospective development of a clinical case study.

In the theoretical block, a systematic literature review format was used, focused on peer-reviewed publications indexed in the Scopus, Web of Science, and PubMed databases. The search strategy was focused on

identifying preclinical and clinical studies describing the molecular mechanisms of non-injection regeneration. Additionally, to compare and refine quantitative and market parameters, a content analysis of industry analytical reports was conducted, which made it possible to verify the statistical and market data used.

Case study analysis: Practical verification and empirical illustration of the theoretically reconstructed mechanisms were carried out through a retrospective analysis of the provided data set on the multidevice protocol DermaReboot Protocol. The analytical procedure included the deconstruction of the nine-stage structure of the protocol, followed by the interpretation of quantitative indicators obtained in an objective observational study (N=40), conducted using standardized diagnostic devices Cutometer MPA 580, Corneometer CM 825, Visia Skin Analysis, and the 3D scanning system Artec Eva.

Results and Discussion

The traditional paradigm of device-based rejuvenation, primarily with respect to RF technologies, was based on the idea of controlled thermal damage to tissues at temperatures above 45°C. It was assumed that collagen denaturation induced in this way initiates a reparative response of fibroblasts and neocollagenesis. However, current data indicate that a number of noninvasive stimuli, including photobiomodulation (PBM) and microcurrent therapy, act predominantly not as damaging factors but as informational or regulatory signals. They initiate complex physiological cascades at the mitochondrial and epigenetic levels, forming a different quality of cellular response [5].

Photobiomodulation, implemented using low level laser therapy (LLLT) or light emitting diode (LED) irradiation in the red and near infrared (NIR) ranges, is a representative example of nonthermal regulatory exposure. Within the DermaReboot protocol this principle is implemented at Stage 8 using the Celluma PRO platform.

A key feature of PBM is that its biological effect is not due to significant tissue heating. Light quanta in a strictly defined spectral range (630–900 nm) are selectively absorbed by the primary mitochondrial photoacceptor cytochrome c oxidase (CCO), the terminal enzyme of the respiratory chain [5]. Photon absorption increases the efficiency of the electron transport chain, which initiates at least two interconnected processes:

Activation of the respiratory chain is accompanied by an increase in ATP production, providing fibroblasts and other cells with an additional energetic substrate for reparative programs, including collagen synthesis triggered in particular by RF exposure at Stage 3 of the DermaReboot protocol [5].

Increased mitochondrial activity is associated with an expansion of the NAD pool [27]. This co substrate is critically important for the family of NAD dependent deacetylases, the sirtuins, primarily SIRT1 (Sirtuin 1) [8, 27].

Activation of SIRT1 initiates a cascade of epigenetic rearrangements: the enzyme deacetylates histones, altering chromatin architecture, and also modifies a number of key transcriptional regulators, including the FOXO family (Forkhead box protein O), which control cellular responses to oxidative stress, apoptosis, and mechanisms of cellular longevity [7]. It has been shown that PBM therapy can induce large scale epigenetic rearrangements of the histone profile [11] and modulate SIRT1 expression [10].

Therefore, PBM at Stage 8 of the DermaReboot protocol performs not merely the function of a final touch of the procedure but serves as a tool for epigenetic reprogramming of dermal cells toward a regenerative phenotype, relying on energy generated in the mitochondria. Similar in direction, although significantly less studied, regenerative signaling cascades can be initiated via mechanotransduction during exposure to ultrasonic nanostimulation and vibroacoustic fields [28].

The second fundamental biophysical modality in the DermaReboot protocol is electrical stimulation (EMS/NMS, microcurrents), implemented at Stages 3 and 5. Chronological aging and cellular stress are accompanied by disruption of the transmembrane potential (TMP), which leads to a decrease in the efficiency of intercellular communication and the regenerative competence of tissues.

Microcurrent therapy uses currents in the physiological range (microamperes) that are close in magnitude and characteristics to endogenous bioelectric currents that form during tissue healing [14]. At the clinical level the aim of such exposure is normalization and restoration of

TMP. In vitro it has been shown that electrical stimulation (ES) in physiological ranges significantly increases the random migratory activity of human dermal fibroblasts [14] and accelerates tissue regeneration processes [12].

In the logic of the synergistic protocol PBM at Stage 8 provides cells with energetic support in the form of increased ATP synthesis, whereas microcurrents at Stages 3 and 5 promote restoration of the electrical lattice of the tissue and the membrane potential [13]. Taken together this creates conditions for effective intercellular signaling, directed migration of fibroblasts, and maintenance of adequate muscle tone, which collectively enhances the regenerative potential of the dermis.

A summary of noninjectable biophysical modalities and their molecular targets is presented in Table 1 below.

Table 1. Summary of non-injectable biophysical modalities and their molecular targets (compiled by the author based on [5, 9, 12, 30]).

Modality (Example in DermaReboot)	Primary target	Secondary biochemical effect	Epigenetic / regulatory modulation
Photobiomodulation (PBM/LED) (Stage 8)	Cytochrome c oxidase (mitochondria)	ATP synthesis	SIRT1 activation, FOXO modulation
Microcurrent therapy (NMS/EMS) (Stages 3, 5)	Ion channels / membrane potential	ATP synthesis (local), intracellular Ca	Fibroblast migration, ECM expression
Radiofrequency (RF) (Stage 3)	Water / dermal collagen	Controlled thermal stress	Heat shock protein (HSP) expression, neocollagenesis

The efficacy of regenerative therapy is determined not only by the degree of activation of endogenous cell populations (primarily fibroblasts), but also by the ability to provide transepidermal delivery of exogenous signaling molecules (cargo) across the epidermal barrier.

A key limiting component of any non-injection technique remains the stratum corneum, which functions as a highly organized diffusion barrier. In this context, the prospects are associated with the development of smart nanoplatforms implementing the concept of responsive delivery [15]. Such systems, as a rule based on hydrogels or nanolipid carriers, are designed in such a way as to release active agents (for example, peptides or growth factors) in response to specific skin microenvironment triggers, such as changes in pH, temperature, and others [15]. A characteristic example is chitosan microneedle systems integrated with thermosensitive hydrogels, in which drug release is initiated upon contact with warm skin [15, 16].

Analysis of a synergistic procedure such as DermaReboot allows the assumption that a multimodal protocol in fact creates conditions for responsive delivery even without the direct use of nanoplatforms:

– Change in pH (Trigger 1): Stage 2 (hydrodermabrasion with an acidic serum) induces a short-term and controlled decrease in skin surface pH.

– Change in temperature (Trigger 2): Stage 3 (RF lifting combined with IR heating) generates a local temperature gradient in the dermis.

– Barrier disruption: Stage 1 (dermaplaning) and Stage 2 (hydrodermabrasion) provide mechanical and chemical thinning of the stratum corneum, thereby increasing its permeability.

– As a result, the subsequent application of peptide complexes (Stage 4, oxygen infusion) and growth factors (Stage 6, mask) occurs under conditions of a deliberately modified microenvironment (reduced pH, elevated temperature), which substantially

enhances their penetration and bioavailability and functionally reproduces the principles of smart adaptive delivery.

If PBM and RF function as an initiating signal for the launch of the regenerative cascade, then the role of cargo in this system is played by cell-free regenerative agents, namely biomimetic peptides and exosomes.

Exosomes are nanovesicles with a diameter of about 30–150 nm, which constitute a key structural and functional element of the cellular secretome [18]. They transport a set of biologically active molecules, including growth factors (EGF, IGF, analogous to those used at Stage 6 of the DermaReboot protocol), mRNA, microRNA, and peptides, acting as a highly specialized system of intercellular communication required for the maintenance of tissue homeostasis and directed restoration of the extracellular matrix (ECM). The use of topical peptides and growth factors [29, 30] (Stages 4 and 6) essentially represents an attempt to therapeutically reproduce the parameters of this natural regenerative secretome.

Further development in this area is associated with bioengineered 3D models of living skins. In such models, non-injection stimuli, including optoelectronic systems and piezoelectric biomaterials responsive to ultrasound exposure [17, 31], will be integrated directly into the matrix. This should provide highly accurate spatiotemporal control over cellular architectonics and regeneration dynamics in a mode as close as possible to real time.

Bridging the gap between the theoretical description of molecular mechanisms and the implementation of technologies in clinical practice requires rigorous objective verification. The data from an observational study of the DermaReboot protocol (N=40, women aged 35–55 years, a course of 4 procedures) create such an opportunity. Table 2 presents the key objective parameters recorded before the start and upon completion of the 30-day course.

Table 2. Objective assessment of the effectiveness of the DermaReboot protocol (N=40) before and after the course of procedures (authors' data).

Parameter (Method / Device)	Before the procedure (Mean value)	After 4 procedures (Mean value)	Change (Abs. / %)
Skin hydration (Corneometer CM 825)	38.2 units	61.5 units	+23.3 units / +61%
Elasticity (Cutometer MPA 580, R2)	0.42 coeff.	0.62 coeff.	+0.20 coeff. / +47%
Wrinkle depth (nasolabial area) (Visia Skin Analysis)	0.85 mm	0.49 mm	−0.36 mm / −42%
Facial oval tone (3D scan Artec Eva)	—	—	+33% lifting (relative to the baseline model)
Pigmentation index (Visia, Melanin Index)	112 units	79 units	−33 units / −29%

Below, Figure 1 presents the dynamics of changes in skin hydration and elasticity parameters according to the DermaReboot study data.

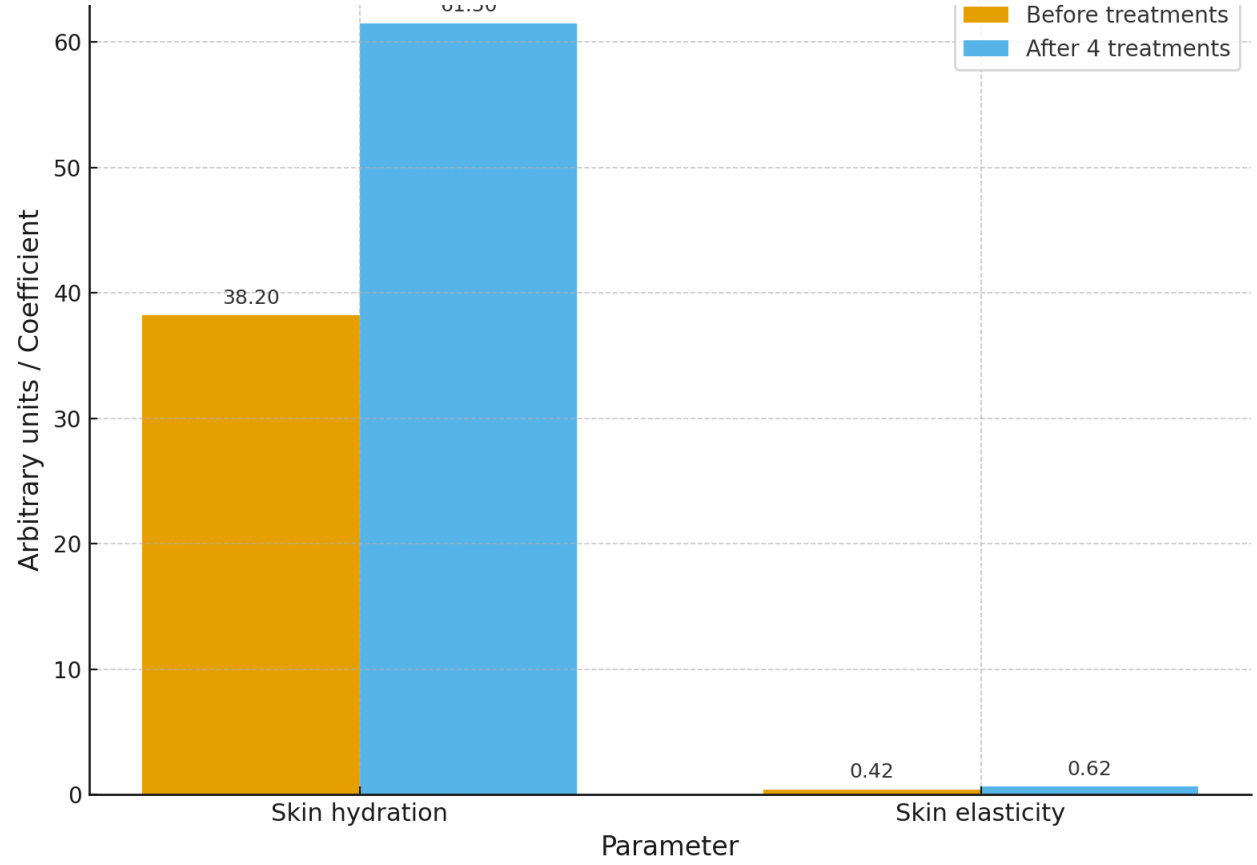

Fig. 1. Dynamics of changes in hydration and elasticity indicators according to the DermaReboot study (N=40) (authors' data).

Figure 2 presents the dynamics of wrinkle depth reduction and improvement of facial contour tone (Artec 3D scan) according to the DermaReboot study data.

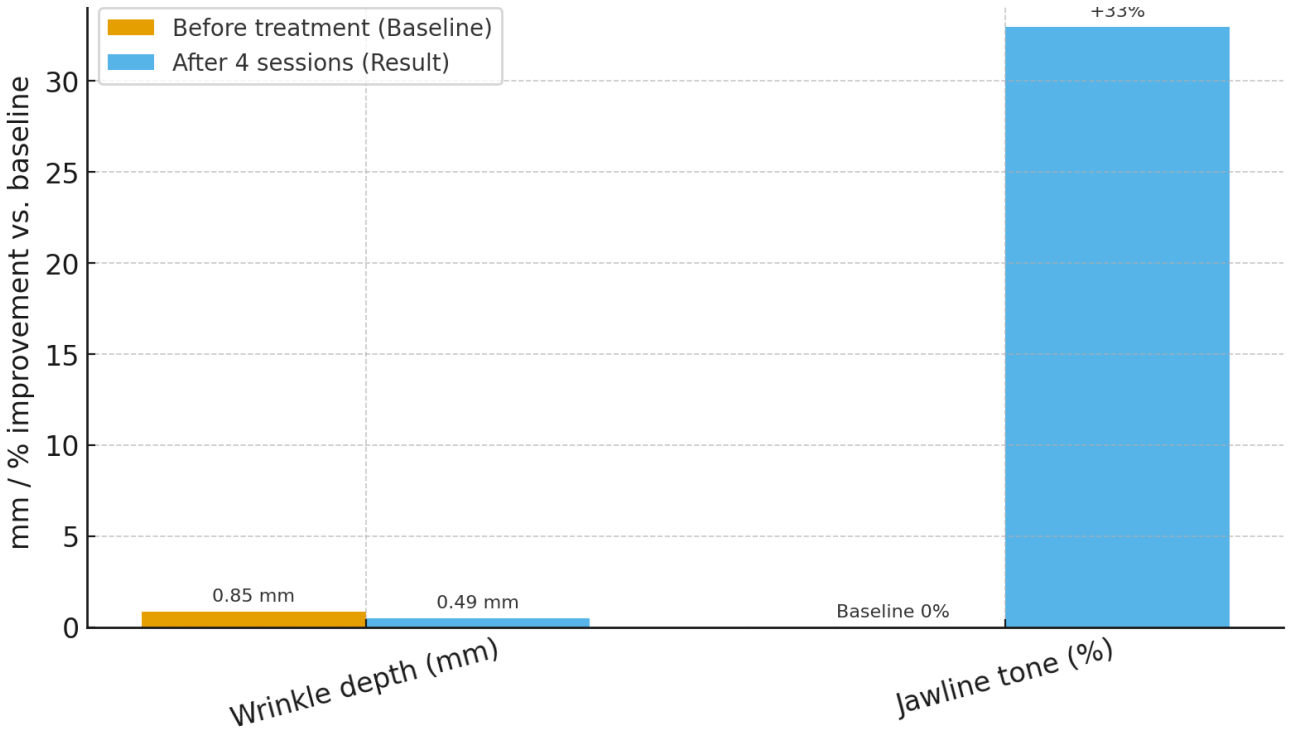

Fig. 2. Dynamics of reduction in wrinkle depth and improvement in oval tone (Artec 3D-scan) according to the DermaReboot study (N=40) (authors' data).

Analysis of the obtained data demonstrates not a linear but a clearly multivector nature of the effect, which serves as an additional argument in favor of the hypothesis of synergism of the protocol's action. The achieved improvements cannot be reduced to the dominance of any one of the mechanisms involved.

Structural changes (a 47% increase in elasticity, a 33% increase in tone) represent a direct consequence of pronounced dermal and myofascial stimulation. They are formed as a result of the combined action of Stage 3 (RF+EMS, providing stimulation of neocollagenesis and reinforcement of the supporting fibrous framework) and Stage 8 (PBM, acting as an energetic donor through increased ATP production for energy-intensive synthetic processes, and also implementing epigenetic modulation, including via activation of SIRT1).

Homeostatic effects (a 61% increase in hydration, a 29% reduction in pigmentation severity) cannot be exhaustively explained by the action of RF or EMS alone. They are the product of a complex protocol that includes exfoliation and preparation of the skin barrier (Stages 1 and 2) in combination with active, responsive non-injectable delivery of hydrating and depigmenting components (peptides, growth factors in Stages 4 and 6).

Each of the specified stages, taken in isolation, is incapable of providing simultaneous statistically significant improvement in all four key vectors: structure, tone, hydration level, and pigmentation parameters. It is precisely the 9-step architecture of the protocol, integrating targeted preparation and modification of the barrier properties of the skin, deep biophysical impact (RF/EMS), epigenetic activation using PBM, and targeted delivery of signaling molecules (peptides), that leads to multilevel restoration of dermal homeostasis, which is evidenced by the aggregate improvement of all recorded parameters [24, 26].

At the same time, despite the demonstrated clinical and experimental potential, large-scale implementation of non-injectable regenerative medicine into everyday practice encounters a number of systemic limitations and barriers. Market dynamics, on the contrary, indicate high and steadily increasing demand: the segment of regenerative agents, including skin boosters (among them PDRN and exosomes), demonstrates a projected compound annual growth rate (CAGR) of about 8.6% for 2025–2033 [20], which underscores the economic feasibility and relevance of developing effective non-injectable delivery systems for such products. Below, Figure 3 presents the forecasted growth of the market for non-invasive aesthetic devices for 2024–2030.

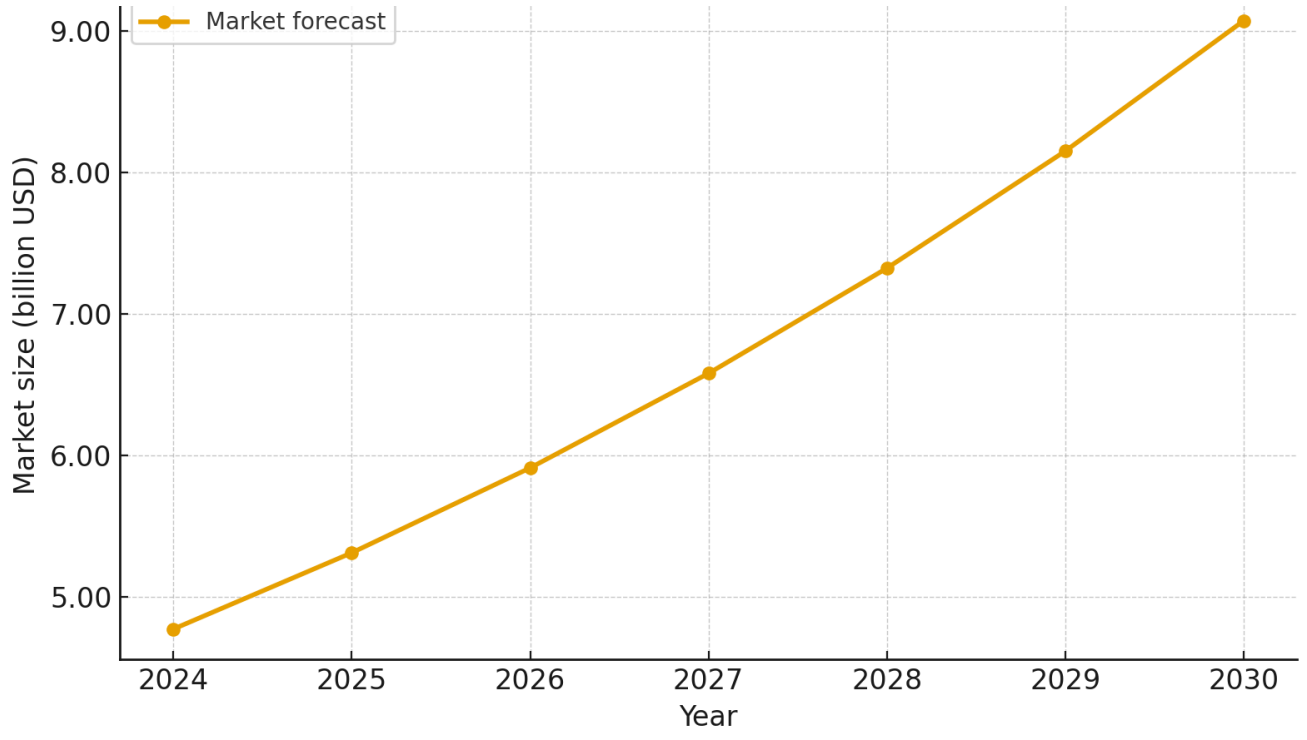

Fig. 3. Forecast for growth of the market of non-invasive aesthetic devices (2024–2030) (compiled by the author based on [4]).

The key systemic limitation lies in the regulatory domain. Paradoxically, the most promising direction of non-injectable regeneration, acellular technologies (exosomes), simultaneously constitutes its main limiting factor.

A pronounced gap exists between the potential of exosomes demonstrated in experimental and early clinical studies [18] and their legally sanctioned, standardized clinical application. As of 2024, exosome therapy has not received approval from either the FDA or the EMA for dermatological and aesthetic indications [23].

The situation is further complicated by the fact that exosomes are formally classified as biological medicinal products [25], whereas detailed regulatory frameworks and harmonized requirements for manufacture and quality control in the GMP (Good Manufacturing Practice) format are lacking [25]. As a result, a gray market of unlicensed products is emerging, the use of which is associated with potential risks for patients and simultaneously hampers the conduct of proper, rigorously planned scientific studies.

The second fundamental barrier is related to the level of evidence. Most regenerative technologies (including stem cell therapy) currently remain highly cost-intensive, while their clinical effectiveness demonstrates substantial variability determined by individual genetic characteristics and the somatic status of the patient [6].

An additional limiting factor is the deficit of data on long-term efficacy and safety for a wide range of device-based methods, particularly in the segment of home-use devices [22]. A significant proportion of the available studies, including the case study analyzed here, is short-term in nature (approximately 30 days of follow-up) and/or conducted in observational designs. This underscores the pronounced need for further large-scale randomized controlled trials (RCTs) specifically focused on the evaluation of multimodal synergistic protocols.

Conclusion

The present study demonstrates that the evolution of regenerative aesthetic medicine is characterized by a transition from an injection-oriented paradigm focused on the correction of clinical manifestations to non-injection strategies aimed at the restoration and maintenance of dermal homeostasis as the primary therapeutic priority.

The clinical efficacy of non-injection protocols (PBM, microcurrents) is determined not only by controlled thermal effects, but also by their function as biophysical regulators capable of retuning key cellular processes. It has been shown that these modalities modulate mitochondrial ATP synthesis and epigenetic expression via the NAD–SIRT1–FOXO cascade, which allows them to be regarded as tools for fine regulation of the cellular response rather than merely as sources of physical stimulation.

Clinical analysis of the multimodal protocol demonstrated objective, multiparametric efficacy: an increase in skin elasticity by 47%, an increase in hydration level by 61%, with a simultaneous reduction in wrinkle depth by 42%. This profile of changes is fundamentally unattainable when each modality is used in isolation and reflects the result of a carefully designed protocol architecture integrating sequential preparation of the skin barrier, deep stimulation, epigenetic activation, and adaptive delivery of functional cargo.

The most promising components, such as exosomes, are currently almost unavailable for widespread legal clinical practice due to the lack of approval by the FDA/EMA and established GMP standards, which significantly slows their translation from the experimental domain into routine clinical practice.

The practical significance of this work lies in demonstrating that carefully engineered synergistic protocols (for example, DermaReboot) can function as a translational bridge between already approved and well-studied technologies (RF, LED, EMS) and promising directions in cellular regenerative medicine. Such protocols provide clinicians with the opportunity to achieve physiologically justified and sustainable restoration of dermal homeostasis under current regulatory conditions, relying on the existing range of device-based and topical modalities.

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