doi:10.36849/JDD.10041e

BRIEF COMMUNICATION Journal of Drugs in Dermatology

Extracellular Matrix Remodeling as a Driver of Skin Tightening and Skin Quality: TriHex+ and Device-Assisted Delivery

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INTRODUCTION

Skin aging involves the gradual breakdown of the ECM's structure and function, including collagen fragmentation, elastin disorganization, and loss of ground substances like hyaluronic acid.[1,3–5] These changes lead to decreased tensile strength, reduced elastic recoil, and increased tissue laxity.[1,3–4] Elastin plays a key role in skin elasticity, but the idea that boosting elastin alone directly causes skin tightening lacks strong biomechanical evidence.[1–2,6] It's important to distinguish elasticity from tightening when evaluating regenerative topical treatments and device-based rejuvenation results, especially with new ECM-related technologies like TriHex+.[8,10,13–15]

MATERIALS AND METHODS

This manuscript synthesizes biomechanical principles, histologic observations, and clinical literature to construct a conceptual model of ECM-driven skin tightening.[1–3,8,10]

Biomechanical Discussion

Biomechanical roles of ECM components

Collagen provides tensile strength and dominates the higher-stiffness part of the stress–strain response, making it the main contributor to structural tightening when fibers contract or the dermis densifies.[3–4,8,11–12] Elastin mainly functions in the low-stiffness region, allowing recoil and resistance to permanent deformation (creep).[1–2] Ground substance, especially hyaluronic acid, adds hydration, viscoelasticity, and turgor, while the DEJ supports anchoring and reduces interlayer shear.[3–4,7]

Elastin in Aging and Regeneration

Aging and photodamage cause elastin fragmentation, solar elastosis, and disruption of fibrillin microfibrils, which together impair recoil and promote microfolding and crepiness.[1–2,6] Restoring organized elastic fiber architecture is therefore expected to improve recovery after deformation and reduce creep.[1–2,6]

Why does elastin alone not tighten skin?

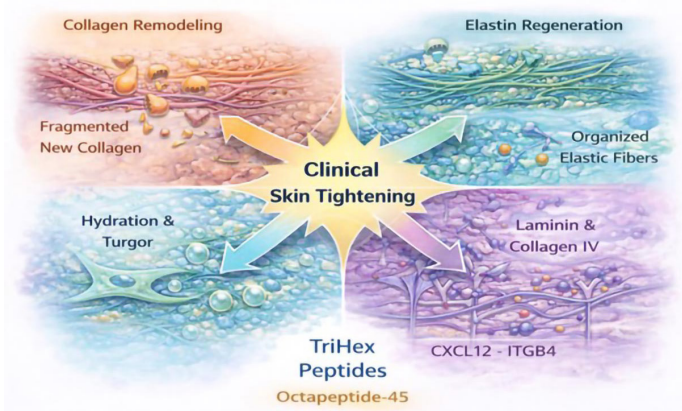
True clinical tightening usually requires one or more of the following: collagen contraction caused by radiofrequency, ultrasound, or laser energy; dermal densification through new collagen growth; structural repositioning or volume redistribution.[8–12] Elastin improves recoil and resilience but does not generate the force needed for lifting or visible contraction.[1–2]

Integrated ECM model

Clinical tightening is best understood as an emergent biomechanical result caused by collagen remodeling, elastin regeneration, increased hydration/turgor, and DEJ reinforcement acting together rather than as a single isolated pathway.[1,3–4,8,13]

Additional biological layers include basement membrane reconstruction (laminin, collagen IV), keratinocyte and fibroblast activation, stem cell recruitment (e.g., CXCL12), and anti-senescent signaling, leading to improved biomechanical performance without directly generating contractile force.[19,23]

FIGURE 1. Multicomponent ECM pathways driving clinical skin tightening (TriHex+ Model).



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TriHex+ Technology as a Model of Multicomponent ECM Remodeling

TriHex Technology is a peptide-based system designed to repair ECM dysfunction by helping to remove damaged collagen and elastin while promoting the growth of new fibers. The original TriHex peptide blend enables sequential ECM recycling, including breaking down fragmented collagen and elastin and replacing them with new, well-structured fibers.[13,17] This process effectively transforms a degenerative ECM environment into a regenerative one.

The addition of Octapeptide-45 (TriHex+) boosts HA production (via CD44 upregulation), improves elastin organization, enhances basement membrane signaling, and promotes fibroblast function, with increased expression of genes like LAMA3, ITGB4, MERTK, and S100A2.[13] These findings support a system-wide ECM modulation rather than an effect limited to a single pathway.

How does this translate clinically? When elastin-targeting therapies are primary, crepey texture and perceived firmness may improve; when collagen contraction and dermal remodeling dominate, visible tightening and lifting are more likely. Optimal outcomes are achieved when regenerative topical support is combined with procedures that create measurable structural change.[8–12,14–16]

The clinical significance of extracellular matrix (ECM) remodeling goes beyond structural biology to include visible improvements in skin quality. Studies evaluating TriHex-based formulations show measurable enhancements in skin texture and roughness through three-dimensional imaging analysis, along with improvements in elastic recoil and retraction dynamics, and increases in dermal thickness as measured by ultrasound.[16,17]

Histologic analyses further confirm increases in collagen, elastin, and hyaluronic acid, supporting true matrix regeneration rather than transient cosmetic effects.[16,17]

In a prospective randomized study, TriHex-treated skin showed increased mucopolysaccharide levels, indicating new collagen formation, along with enhanced elastin fiber development in the papillary dermis. It also exhibited increased CD44 expression, signaling upregulation of hyaluronic acid pathways, and was accompanied by noticeable reductions in skin roughness and smoother skin overall.[16]

These findings support the idea that ECM correction directly leads to noticeable improvements in skin texture, resilience, and elasticity, reinforcing the concept that enhancing skin quality results from underlying matrix optimization.[16,17]

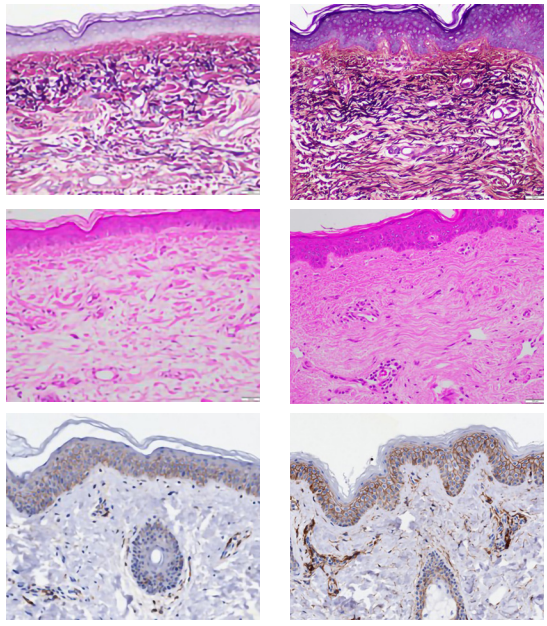
Clinical Implications

Clinicians should view elastin-directed therapies as enhancing skin quality, resilience, and recovery rather than as primary methods for tightening. Combining ECM-optimizing topicals with energy-based devices provides a logical approach to improving both biomechanical performance and visible laxity.[1–2,8–12]

Clinical Translation and Procedural Synergy of TriHex+

Preconditioning with TriHex+ before procedures enhances ECM organization, reduces inflammatory burden, and improves healing speed and overall skin quality. In a randomized split-face facelift study, preconditioning led to significant increases in collagen, elastin, and hyaluronic acid, reversal of solar elastosis, and better healing outcomes.[14] Procedural pairing studies show faster healing, less edema and exudation, improved barrier recovery, and higher patient satisfaction.[15] Additional controlled studies confirm histologic increases in collagen, elastin, and hyaluronic acid, and strengthening of the DEJ, supporting true ECM regeneration rather than temporary cosmetic effects (Figure 2).[16]

FIGURE 2. A 55-year-old female, biopsy from preauricular area of face, the left side pre-treatment baseline, the right side 4 weeks after start of topical TriHex technology.



Top: Movat stain demonstrating elastic fibers (black). Left baseline shows short and disorganized with foci of "clumping" consistent with solar elastosis. Right shows after treatment, elastic fibers are organized horizontally, increased in amount, and are elongated and healthy. Middle: Hematoxylin Eosin stain demonstrating reconstitution of ECM. Left: HE-stained sections show solar elastosis of the dermis with voids of homogeneous elastotic material. The overlying epidermis shows effacement of the rete ridges and a poorly defined DEJ. Right: there is significant replacement of sparse ECM with significant replacement with dense collagen fibers and complete transformation of the ECM. Early start of new rete ridges is evident with strengthening and more definition of the DEJ, Bottom: CD44 immunohistochemical staining. Left: highlights hyaluronic acid receptors of the keratinocytes and the fibroblasts. Right: after treatment, there is increased CD44 staining in keratinocytes, which represents up-regulation of CD44 receptors in both epidermal cells and fibroblasts.

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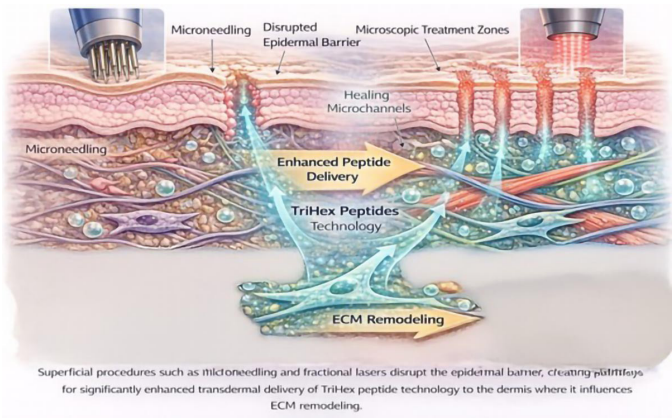
FIGURE 3. Device-assisted delivery of ECM-modulating peptides.



Device-Assisted Delivery of ECM-Modulating Peptides

Historically, TriHex-based formulations have been used for preconditioning and post-procedural healing, especially after deeper ablative interventions.[14,16] These applications leverage TriHex's ability to: reduce fragmented extracellular matrix components; promote collagen and elastin regeneration; accelerate wound healing; restore overall dermal structure.

However, new procedural trends favor superficial, low-downtime treatments such as microneedling, fractional non-ablative laser (eg, Halo), and radiofrequency-based therapies.[8,12] These methods cause controlled micro-injuries at a more superficial level, resulting in quick recovery but less direct structural remodeling. In this context, these devices can be seen as facilitators of transdermal delivery rather than just remodeling tools. The mechanisms of enhanced delivery with these superficial procedures involve temporary disruption of the stratum corneum and epidermal barrier, creating microchannels (microneedling), microscopic treatment zones (fractional lasers), and thermal or mechanical permeability changes. These alterations enable better penetration of topically applied agents into deeper layers of the epidermis and dermis, a concept often described as laser-assisted or device-assisted delivery. This allows for improved penetration of peptide-based technologies such as TriHex+ into deeper dermal layers, boosting interaction with fibroblasts and ECM remodeling pathways.[18–21]

This concept, often called laser-assisted or device-assisted delivery, helps topical agents bypass the stratum corneum and reach target tissues more effectively. For ECM-modulating peptides, this improves collagen production, elastin organization, hyaluronic acid synthesis, and the strength of the dermal–epidermal junction.[18–21]

A three-phase treatment approach is recommended: preconditioning with TriHex+, device-assisted delivery through superficial procedures, and post-treatment maintenance. This combined method fosters ongoing ECM remodeling and enhances skin quality. For peptide-based systems like TriHex+, this has significant theoretical implications:

- Increased delivery to fibroblast-rich dermal areas
- Better interaction with ECM components and remodeling pathways
- Improved access to basement membrane and DEJ signaling regions

Therefore, superficial procedures may serve as biological amplifiers, boosting the effective concentration and activity of peptides within target tissues.

This delivery-based model closely aligns with the evolving understanding of aging biology. Notably, recent expansions of the "Hallmarks of Aging" framework now recognize extracellular matrix dysfunction as a key component of tissue aging.[23]

Within this framework, TriHex+ can be positioned as a direct modulator of ECM aging, acting through:

- ECM recycling (fragment clearance → regeneration)
- Collagen and elastin restoration
- Hyaluronic acid upregulation
- Basement membrane and DEJ reinforcement
- Anti-senescent signaling

CONCLUSION

Elastin regeneration improves recoil and reduces tissue creep; however, clinically meaningful skin tightening remains a complex phenomenon that requires concurrent collagen remodeling and structural support. Elastin should be seen as a supportive contributor rather than the sole factor driving tightening.[1–2,8,10–12,13]

These findings support a broader understanding: that improvements in skin texture, tone, and resilience are directly linked to ECM correction, rather than just superficial effects. Technologies like TriHex+ serve as a bridge between molecular remodeling and visible aesthetic results.

These technologies demonstrate a systems-level approach to skin rejuvenation by modulating collagen, elastin, hyaluronic acid, and the integrity of the dermal–epidermal junction, ultimately enhancing biomechanical performance without directly generating contractile force.

Device-assisted delivery of ECM-modulating peptides combines procedural dermatology with biologic therapy, where superficial treatments enhance the dermal bioavailability of regenerative signals, leading to improved extracellular matrix remodeling and notable enhancements in skin quality and resilience.

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TABLE 1.

Three-phase therapeutic model to reconstitute ECM through delivering TriHex technology

Phase	Objective	Mechanism of Action	Clinical Effect
1. Preconditioning Phase (Biologic Optimization)	Prepare ECM environment prior to intervention	• TriHex+ initiates ECM recycling (clearance of fragmented collagen/elastin) • Reduces inflammation and oxidative burden • Enhances fibroblast function and baseline dermal health	• Improved tissue readiness • Reduced procedural inflammation • Enhanced healing response
2. Device-Assisted Delivery Phase (Augmentation)	Enhance dermal penetration of active peptides	• Superficial procedures (microneedling, fractional laser, RF) create transient microchannels • Disruption of epidermal barrier increases permeability • Facilitates deeper delivery of TriHex peptides to fibroblast-rich dermis • Amplifies ECM signaling pathways	• Increased bioavailability of peptides • Enhanced collagen/elastin/HA stimulation • Accelerated biologic response
3. Post-Procedural Maintenance Phase (Sustained Remodeling)	Sustain ECM regeneration and clinical improvements	• Continued TriHex application supports ongoing ECM remodeling • Reinforces collagen synthesis and elastin organization • Maintains hyaluronic acid production and DEJ integrity • Supports anti-senescent signaling pathways	• Improved skin texture and tone • Enhanced elasticity and resilience • Long-term maintenance of skin quality and tightening effects

DISCLOSURES

Dr. Widgerow is the Chief Scientific Officer of Galderma. The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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