Research in Focus:

Exploring a Layered Mechanical-Biological Model for Hybrid PEG-HA Fillers

A recently published study investigates whether PEG-crosslinked hyaluronic acid systems may support coordinated mechanical and biological regeneration

A proof-of-concept study published in the Journal of Applied Cosmetology by Basso et al. outlines a conceptual framework for facial rejuvenation using polyethylene glycol (PEG)-crosslinked hyaluronic acid combined with low-concentration calcium hydroxyapatite (CaHA).[1] The formulation discussed in the paper corresponds to a commercially available PEG-crosslinked HA + CaHA hydrogel.

The authors propose that this hybrid PEG-HA + CaHA system may enable immediate structural reinforcement alongside progressive tissue remodelling within a single scaffold. The paper

frames this interaction within a broader discussion of mechanobiology and physiological regeneration.

Mechanical and biological coordination

Central to the study is the concept that mechanical support and biological stimulation may occur concurrently within the same injectable matrix. The authors refer to this integrated framework as the 'Dual Core' protocol, reflecting the proposed coordination between structural reinforcement and biological activation.[1]

The PEG-crosslinked hyaluronic acid component provides immediate structural reinforcement through cohesive gel deposition, intended to restore contour and maintain localised tissue tension.[1] Unlike most conventional hyaluronic acid fillers, which are stabilised using 1,4-butanediol diglycidyl ether (BDDE), PEG crosslinking produces a chemically distinct hydrogel network. This difference in crosslinking chemistry is relevant because it influences gel architecture, cohesivity and potentially the way the material interacts with surrounding tissue.

The authors reference in vitro and histological studies suggesting that PEG-crosslinked HA may be associated with reduced macrophage recruitment and lower expression of certain pro-inflammatory cytokines when compared with traditional systems.[1]

The calcium hydroxyapatite component, present at low concentration, is proposed to stimulate fibroblast activation and collagen remodelling. Cited data include increased collagen fluorescence intensity at 21 days, together with reduced CD4+/CD8+ inflammatory-cell infiltration and normalisation of tissue architecture.[1]

Within the proposed framework, mechanical lift and biological activation are not described as separate phases but as coordinated processes occurring within the same scaffold environment, with the gel matrix providing structural stability while CaHA particles contribute to progressive extracellular matrix (ECM) remodelling.

Layered anatomical application

Beyond material composition, the study outlines a structured injection approach designed to align with facial anatomy.

The authors describe superficial or mid-fat layer placement of the PEG-HA + low-dose CaHA formulation using small micro-depots delivered via cannula.[1] This layer is intended to support dermal tension while facilitating controlled biological stimulation within the extracellular matrix. By distributing the material in limited volumes, the framework emphasises restoration of tissue integrity rather than overt augmentation.

In addition, deeper placement of a higher-elasticity PEG-crosslinked HA filler in supraperiosteal or sub-SMAS planes is described as providing structural reinforcement and supporting lifting vectors.[1] This deeper scaffold is positioned as optimising the anatomical environment for the more superficial regenerative activity.

The authors frame this two-plane strategy within a conservative-volume philosophy, advocating anatomical precision and layered support rather than high-volume correction. As presented, the technique reflects a broader shift within regenerative aesthetics toward targeted compartment-based treatment and tissue harmonisation.

A proposed metabolic dimension

In addition to mechanical support and fibroblast stimulation, the authors introduce a further conceptual element described as a potential metabolic dimension.

Drawing on emerging literature, the paper discusses the possibility that hyaluronic acid and calcium hydroxyapatite may influence communication between dermal fibroblasts and subcutaneous adipocytes.[1] This includes reference to potential modulation of exosome signalling and pathways associated with adipocyte metabolism and tissue homeostasis.

Supporting histological evidence cited within the paper includes findings from Kubik et al. (2024), who reported a 27.3% increase in collagen fluorescence intensity 21 days following treatment with PEG-HA + 1% CaHA, together with reduced CD4+/CD8+ inflammatory infiltration and normalisation of tissue architecture.[2] These observations reinforce the biological remodelling component of the framework and contribute to the broader discussion of coordinated tissue interaction.

Within this context, the metabolic dimension is presented as an extension of the mechanical-biological model, reflecting an expanding understanding of dermal-adipose communication. Further

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investigation will help clarify how these interactions may influence long-term tissue homeostasis.

Preliminary observations and interpretation

In preliminary clinical application of the described protocol, the authors report immediate contour improvement following treatment, with progressive enhancement in skin density and elasticity observed over a 4-6 week period.[1] No palpable nodules or significant adverse events were described within the follow-up outlined.

As presented, the framework integrates three interconnected components: mechanical reinforcement through PEG-crosslinked HA, biological stimulation via low-dose CaHA, and a proposed metabolic interaction within the dermal-adipose interface. The authors position this layered model within a broader shift in aesthetic medicine toward physiology-led regeneration and anatomically guided treatment strategies.

Future evaluation using objective imaging modalities, such as high-frequency ultrasound and three-dimensional assessment, is proposed to further characterise structural and tissue-level changes over time.

For practitioners, the paper contributes to the ongoing discussion around how chemically distinct HA systems may interact with tissue beyond volumetric correction. Whether the proposed mechanical-biological-metabolic integration translates into measurable long-term clinical advantages will continue to be explored as further data emerge.

In Practice: **Nurse Prescriber Emma Ross** on Clinical Application

While the published framework focuses on mechanistic theory and histological findings, nurse prescriber Emma Ross describes how hybrid PEG-crosslinked HA systems translate into day-to-day clinical use.

For Ross, the primary distinction lies in versatility.

"It's unlike other fillers I've used in that I can approach it from both a deep structural and a more superficial regenerative perspective," she explains. "I'm able to use it for deep structural support in patients with age-related volume changes, but also in more superficial planes where I want to encourage biostimulation alongside subtle support."

In her practice, deeper placement is typically performed as a single treatment for structural reinforcement. When used more superficially, she may adopt a short protocol approach, particularly in areas such as lateral facial lines, sometimes combining it with other treatments within a broader regenerative plan.

She views the product less as a volumising tool and more as part of a longer-term tissue strategy. "I'm thinking about tissue quality and support over time, not just replacing volume," she says. "It changes how you plan treatment."

Ross notes that patient expectations require careful management. "There is an immediate effect from the structural component, but I advise patients to allow four to six weeks for full integration and tissue response," she explains, noting, "Patients often respond positively to the concept of collagen stimulation and long-term tissue support."

From a practical perspective, she highlights the material's handling characteristics. "The extrusion force is higher than many traditional fillers, so injectors may need to adjust to that," she says. "However, slower injection can support greater control."

She also reports favourable integration in her experience. "Swelling tends to be controlled and the product integrates smoothly," she notes. "That said, it's still a dermal filler, and anatomical knowledge and careful technique remain fundamental."

Ross typically recommends annual review rather than routine retreatment, with further intervention guided by individual tissue response and ageing progression.

Disclosure: Emma Ross acts as a key opinion leader for Neauvia, the manufacturer of Neauvia Stimulate.

References

1. Basso M, Di Lella E, Marchetti F. Dual Core: A Mechanical, Biological, and Metabolic Model for Physiological Bio-regeneration with PEG-Crosslinked Hyaluronic Acid Fillers. *J Appl Cosmetol.* 2025;43(3):Sept-Dec. // 2. Kubik P, Gruszczyński W. Safety of PEGylated hyaluronic acid filler for the treatment of facial skin aging: case report. *Clin Case Rep Int.* 2024;8:1679.