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Cutaneous biomodulation with hyaluronic acid of different molecular weights: from signaling molecule to clinical skin quality

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ABSTRACT

Introduction: Hyaluronic acid is the most abundant glycosaminoglycan in the cutaneous extracellular matrix, playing a key role in hydration homeostasis, barrier integrity, and wound healing. Recent evidence shows that beyond its humectant effect, hyaluronic acid acts as a signaling molecule, interacting with receptors such as CD44 and RHAMM, and modulating inflammation, cell proliferation, and differentiation. The distribution of molecular weights – high , medium, and low – determines the depth of penetration, receptor affinity, and biological response profile, paving the way for a targeted cutaneous biomodulation approach.

Objectives: To synthesize the biological and clinical evidence on the cutaneous biomodulation exerted by uncross-linked hyaluronic acid of different molecular weights, highlighting: 1) cell signaling mechanisms and effects on the skin barrier; 2) the impact of molar mass on skin penetration and interaction; and 3) clinical outcomes in skin quality and aging.

Methods: A narrative literature review was conducted in the PubMed, Scopus, and Web of Science databases, with no year restriction, using the descriptors “hyaluronic acid”, “molecular weight”, “skin”, “CD44”, “biomodulation”, and “topical”. In vitro and in vivo experimental studies, clinical trials, and reviews evaluating uncross-linked hyaluronic acid in topical formulations or transdermal delivery systems were included, provided they described the molecular weight and structural or functional skin outcomes. Reports exclusively focused on cross-linked fillers or systemic routes were excluded.

Results: Molecular weights – high acts predominantly on the skin surface, forming a moisturizing film, reducing transepidermal water loss, and exerting an anti-inflammatory effect by attenuating the response to UVB and modulating Damage-Associated Molecular Patterns and pro-inflammatory cytokines. Conversely, molecular weights –low demonstrates greater penetration capability into the stratum corneum and epidermis, increases CD44 expression in keratinocytes, and stimulates

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differentiation, lamellar body formation, and barrier homeostasis. Clinical studies with creams containing 50–130 kDa hyaluronic acid demonstrate significant improvement in hydration, elasticity, and a reduction in periocular wrinkle depth within 60 days, outperforming formulations with higher molecular weights. In elderly individuals with xerosis, molecular weights –low proved more effective than molecular weights – high in restoring hydration measured by capacitance, while maintaining safety and tolerability. Formulation technologies, such as hydrogels, nanohydrogels, conjugates, and vectorized systems, enhance the bioavailability of different molecular weights, prolong hydration, and allow hyaluronic acid to be used as carriers for other biomacromolecules.

Conclusions: Cutaneous biomodulation with multi-molecular weight uncross-linked hyaluronic acid represents a mechanistically grounded approach to improving skin quality, enhancing the outcomes of minimally invasive aesthetic procedures. The rational combination of molecular weights – high and molecular weights –low , integrated with appropriate vehicle technologies, allows for the simultaneous modulation of the barrier, inflammation, and tissue remodeling, shaping a promising field for the development of new clinical protocols and dermo-aesthetic products.