Premise

Hyaluronic acid is a key component of connective tissues of humans and other mammals. It gives the skin its unique properties as strength and shape retention. An its lack leads to a weakening of the skin, promoting the wrinkles and blemishes formation. Its concentration in body tissues tends to decline with age.

It is chemically defined as a glycosaminoglycan with a polysaccharide chain produced by the aggregation of thousands of disaccharide units formed in turn by residues of glucuronic acid (a derivative of glucose) and N-acetyl glucosamine. In vivo all the glucuronic acid and N-acetyl glucosamine carboxyl groups are fully ionized, giving to the hyaluronic acid molecule an high-polarity, and thus a high solubility in water. Thanks to this property hyaluronic acid can complex with many molecules of water reaching a high degree of hydration. In the amorphous matrix of connective tissue the acid is responsible to maintain the degree of hydration, the turgidity, the plasticity and the viscosity. It can also act as a cementing substance, as anti-collision molecule and as an efficient lubricant, preventing damage of cells tissue from physical stress.

The half-life of hyaluronic acid is very short, 12-24 hours, in the dermis and in the epidermis (Practical Aspects of hyaluronan-Based Medical Products, Jing-wen Kuo - Taylor & Francis - 2005). Fragments 20-38 monomers, from hydrolysis of the dermal matrix, having stimulated CD 44 are permanently embedded in the cell and metabolized, by hyaluronidase, in precursors. These are then reused, in part, for the resynthesis of new macromolecules.

From the above, the skin needs continuous, daily, synthesis of hyaluronic acid to maintain constant the concentration of this and the dermis hydration. Hence, the aesthetic medicine has worked in the formulation of various treatments using hyaluronic acid to improve the aesthetics of the face.

Today, hyaluronic acid is proposed as:

- Biostimulant
- Filler
- Cosmetic
Biostimulation with hyaluronic acid

The term of biostimulation in aesthetic medicine is used to indicate a skin biological activation with the goal of improving the aesthetic itself. This must mean that the introduction of an active substance in the skin induces a series of metabolic reactions positive for biology and for the aesthetics of the skin itself.

The incorporation of hyaluronic acid in macromolecular form in the skin does not induce a positive response. Indeed, the literature tells us:

- The presence of hyaluronic acid has no effect on the production of endogenous hyaluronic acid (Hyaluronan affects protein and collagen synthesis by in vitro human skin fibroblasts. Croce MA, Dyne K, Boraldi F, Quaglino D Jr, Cetta G, Tiozzo R, Pasquali Ronchetti I. Department of Biomedical Sciences, University of Modena and Reggio Emilia, Modena, Italy)
- 0.5 -1 micro Mole hyaluronic acid induce a reduction of protein synthesis (Hyaluronan affects protein and collagen synthesis by in vitro human skin fibroblasts. Croce MA, Dyne K, Boraldi F, Quaglino D Jr, Cetta G, Tiozzo R Pasquali Ronchetti I. Department of Biomedical Sciences, University of Modena and Reggio Emilia, Modena, Italy)
- High concentration of hyaluronic acid reduce the formation of extracellular matrix (Effects of hyaluronic acid-stimulating factor on viability and collagen synthesis of fibroblasts Wang Q, Lu K, Yang L. Genter Plastic Surgery, Xijing Hospital, Xi’an 710032)
- 1 mg/ml of hyaluronic acid increases the MMP activity and active the latent in matrix (Effect of hyaluronan on MMP expression and activation. Isnard N, Legeais JM, Renard G, L. Robert Laboratoire de Recherche en Ophtalmologie, Esc B3 6eme etage, Hopital Hotel Dieu, 1 Place du Parvis Notre-Dame, Paris 75004, France)

That is, the introduction of preformed hyaluronic acid within the dermis cannot lead to anything but a synthetic and catabolic activity response block. In fact introducing macromolecular hyaluronic acid we give an indication that this component of the dermal matrix is present (and is not required new training) and in excess quantity (and therefore must metabolize the excess).


If we want a biological response that improves the hyaluronic acid concentration, we provide to the dermis the indication that the drug concentration is decreased and this can only be achieved by introducing fragments of hyaluronic acid, index of catabolism macromolecule. The literature tells us, in fact:


with the statement that the hyaluronic acid macromolecular inserted into the skin, even as a filler, induced an biological improvement by a neocollagenogenesis. Again we must make a clarification because the work reported in this statement talked of neocollagenogenesis, but referred to the new formation of fibrotic collagen. Whereas the increase in collagen type I° (fibrotic) is considered a sign of skin aging, there seems wrong to talk about this result as Biostimulant.

Hyaluronic acid such as filler
The fillers are substances used in medicine for the filling and for wrinkles and depressions reduce. For over twenty years, hyaluronic acid has been proposed as filler.

The action of metalloproteinase (hyaluronidase) that lead to rapid degradation of the product has prompted the industry to reduce the hyaluronic acid attack for the metalloproteinase by creating cross- links between the different macromolecular chains.

It began with a two-dimensional cross-links to arrive today to a three-dimensional cross-links. All this has led to a greater resistance to filler metabolism, for difficulties of the hyaluronidase to attack the macromolecule, with a more durable aesthetic result, but with a change in biological response to the product.

In fact, the new three-dimensional structure, staying for a long time in the dermis, leads to a prolonged compression of the tissues that induces a biological response to foreign body. It induce the stimulation of new fibrous tissue (Arch Dermatol. 2007 Feb; 143 (2) :155-63. In vivo stimulation of de novo collagen production Caused by Cross-linked hyaluronic acid dermal filler injections in photodamaged human skin. Wang F, Garza LA, Kang S, Varani J, Orringer JS, Fisher GJ, Voorhees JJ.) that result in a stiff volumetric response, which is evident with unaesthetic granules. The problem is when the granules are only palpable, but becomes important when they are also visible. In fact the solution of this granuloma is only surgical.

This, coupled with the inflammatory response caused by not perfectly free of pyrogens hyaluronic acid, with the immune response leading to the retention of heterologus proteins for incorrect purification and with the problems of mutagenic crosslinking agent (BDDE, eterebutanedioldiglicidico) that should be well removed from the product to avoid cancerogenetico risk, prompted healthcare facilities to begin a study on European territory with the aim of highlighting possible damage arising from use of hyaluronic acid as a filler. (Delayed immune-mediated adverse effects related to hyaluronic acid and acrylic hydrogel dermal fillers: clinical Findings, long-term follow-up and review of the literature. Alijotas-Reig J, Garcia-Gimenez V J Eur Acad Dermatol Venereol. February 2008, 22 (2) :150-61. Review).

Hyaluronic acid as a cosmetic
The transdermal route is one of the routes of entry in our body and shall, as regards the skin, a direct and immediate injection of the substances that are applied topically.

For the hyaluronic acid, we must remember that topical administration of this macromolecule determines only a reduction of the transpiratio insensibilis and improves indirectly skin
hydration. The administration of precursors is still insufficient to improve skin concentration. This is because the precursors (glucuronic acid and N-acetyl glucosamine) are not able to overcome the cell walls and thus cannot be used by skin cells.

The solution to this can be achieved using liposomes.

The liposome is a phospholipid vesicle, which can vary in size between 25 nm and 1μm in diameter. Typically consist of a double layer of phospholipids or cholesterol and are used for the transport of substances into cells. A liposome in fact has an aqueous solution, in which are dissolved hydrophilic solutes, which could not pass directly through cell membranes (which are in fact hydrophobic). The lipid bilayer of liposomes in contact with the cell wall, merges with the lipid bilayer of the plasmalemma and release the content in the cell cytosol.

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