

Hyaluronic acid & polysaccharides – for skin hydration and wrinkle reduction

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Hyaluronic acid is a chain-shaped molecule composed of repetitive sugar-like units. Over the years hyaluronic acid has developed into an almost indispensable component in cosmetic preparations. And news continue to roll in.....

Hyaluronic acid alias hyaluronan fulfills various functions in the human body. As a component of the extracellular matrix it is significant, among others, for the internal pressure of the vitreous body, the synovial fluid of the joints and the cushioning function of the connective tissue. Besides collagen, the latter-mentioned feature of hyaluronic acid makes it an interesting component of anti-aging cosmetics that are supposed to smooth out wrinkles and maintain the elasticity of the skin. The extremely high water-retaining capacity of hyaluronic acid is an essential skin care factor for dry skin.^{1,2}

Just as with collagen, the concentration of hyaluronic acid in the skin declines with age. The aesthetic medicine counteracts the effects of aging with anti-wrinkle injections of hyaluronic acid and its derivatives. Invasive techniques, however, are not allowed in the cosmetic field.

Topically applied...

...hyaluronic acid and its salts have a completely different mode of action compared to that in the interior of the skin. Hyaluronic acid bonds to the keratin of the skin via hydrogen bridges. That is why a light tension can be felt after the application of the substance and the evaporation of the water contained in it. An additional cushioning effect leads to a reduction of the wrinkle depth. Also a pleasant moisturizing film forms on the skin surface.

The polysaccharide group

Hyaluronic acid belongs to the group of polysaccharides, in other words, it is a natural polymer consisting of glucuronic acid- and N-

acetyl-glucosamine units. Glucuronic acid, a saccharic acid, is an oxidation product of glucose and detoxifies the body by transforming unwanted materials into water-soluble substances and then releasing them out of the body via liver, kidneys and through urine. N-acetyl-glucosamine is a compound of acetic acid with the amino sugar glucosamine which is assumed to have life-prolonging features.³ Hence glucosamine as well as N-acetyl-glucosamine can be found in a whole variety of food supplements.

Manufacturing and storage

The manufacturing of hyaluronic acid from cockscombs has stopped for quite some time now. Today the substance is produced with biotechnological methods with the help of streptococcus zooepidemicus cultures. In comparison with the original products, these manufacturing processes allow high-purity and protein-free products with excellent tolerability. Polymers with a molecular mass of several million Dalton (Da) can thus be obtained. 1 Dalton is the equivalent of $1.66 \cdot 10^{-27}$ kg.

Optimal molecular size

Discussions on the optimal size of hyaluronic acid molecules for cosmetic applications are still going on. Wishful dream is to externally apply hyaluronic acid on a deficient dermis and achieve similar effects as known from endogenous hyaluronic acid. This certainly implies the passage through the skin barrier. Experimental studies with fragmented hyaluronic acids show that a molecular size of 50,000 and of 130,000 Dalton leads to improved skin hydration, skin elasticity and reduced wrinkle depth.⁴ These

¹ Lautenschläger H, Hyaluronsäure – ein legendärer Wirkstoff, Kosmetische Praxis 2008 (4):16-18

² Hyaluronsäure und Haut in Trends in Clinical and Experimental Dermatology (Volume 3), Volume Editors: Wohlrab W, Neubert RRH, Wohlrab J, Shaker Verlag, Aachen 2004

³ Bell, GA et al.: Use of glucosamine and chondroitin in relation to mortality. In: Eur J Epidemiol 2012 (27):593-603

⁴ Pavicic T, Gauglitz GG, Lersch P, Schwach-Abdellaoui K, Malle B, Korting HC, Farwick M: Efficacy of cream-based novel formulations of hyaluronic acid of different molecular weights

effects imply that shorter hyaluronic acid chains might pass through the skin barrier.⁵ It should however be mentioned that the sizes stated above just are average values covering a smaller or broader particle size distribution. It is possible that significantly smaller or larger fragments are contained in the material used. This unfortunately has not been studied in detail.

The smallest fragments finally are the above mentioned glucuronic acid particles with 194 Da, N-acetyl-glucosamine with 221 Da and possibly even glucosamine with 179 Da. Molecules of this size can pass through the skin barrier – all the more in presence of penetration enhancers. Moreover, it has to be reckoned that hyaluronic acid is fragmented by hyaluronidases, in particular hyaluronate lyases and secondary enzymes of the individual microbiome of the skin; these fragments may possibly stimulate the endogenous hyaluronic acid production after their passage through the skin barrier.^{6,7} What is sure, however, is that fragmented hyaluronic acid as such in the above mentioned size and also smaller cannot induce this process.

Based on its high microbial sensitivity and its hygroscopic features it is essential that pure hyaluronic acid, a colourless powder, has to be stored under absolutely dry and sterile conditions.

Applications in the field

In practice, hyaluronic acid is frequently used in combination with ultrasonic treatments. Minor amounts of low molecular fragments form in this context and their penetration cannot be excluded. Hyaluronic acid is disadvantageous insofar as it is easily removed after cleansing the skin with water. In other words, it needs to be reapplied again and again in order to maintain the effects.

Hyaluronic acid as a physiological substance is applicable in the form of an aqueous lubricant

in anti-wrinkle treatment. In: *Journal of Drugs in Dermatology* 2011 (10);9:990–1000

⁵ Kaya G, Tran C, Sorg O et al: Hyaluronate fragments reverse skin atrophy by a CD44-dependent mechanism. *PLoS Med* 3 (2006) e493

⁶ Uitterlinden EJ, Koevoet JLM, Verkoelen CF, Bierma-Zeinstra SMA, Jahr H, Weinans H, Verhaar JAN, and van Osch GJVM, Glucosamine increases hyaluronic acid production in human osteoarthritic synovium explants, *BMC Musculoskelet Disord*. 2008;9:120

⁷ Sayo T, Sakai S, Inoue S, Synergistic effect of N-acetylglucosamine and retinoids on hyaluronan production in human keratinocytes, *Skin Pharmacol Physiol*. 2004 Mar-Apr;17(2):77-83

gel in the case of vaginal dryness. A less expensive alternative here is xanthan (food additive E 415) which also belongs to the group of polysaccharides. The combination of hyaluronic acid and xanthan is an excellent gel base for low-fat or non-fat facial preparations.

Endogenous hyaluronic acid

There are alternatives for the attempt of transporting hyaluronic acid or its fragments through the skin barrier as for instance the stimulation of endogenous hyaluronic acid production or the inhibition of its degradation:

1. Stimulation of hyaluronic acid synthesis through
 - glucosamine or N-acetyl-glucosamine – as described above
 - phytohormones
 - saponins resp. saponinins
2. Inhibition of the endogenous hyaluronidases through
 - sugar-related substances
 - saponins resp. saponinins

Since some of the active agents in question are smaller molecules, the passage through the skin barrier also is far easier, in particular when using carrier systems such as liposomes and nanodispersions. Stimulative (1) phytohormones (isoflavonoids) occur e.g. in soybean- and red clover extracts, saponins and Co. in the form of ruscogenin and ruscogenin can be found in butcher's broom extract (*Ruscus aculeatus*).

Degradation-inhibiting substances (2) are for instance heparin, pectins (e.g. found in apples) and the alginic acids of brown alga such as *Laminaria digitata*. These saccharide derivatives however have a high-molecular structure similar to hyaluronic acid. In the case of liquorice root saponins such as glycyrrhizin and glycyrrhetic acid (aglycon) as well as aescin gained from horse chestnuts (alias buckeyes), conditions are far more favourable. As for all the other substances mentioned, the in-vitro evidences dominate here too.

Nevertheless, the substances mentioned match very well with hyaluronic acid for the use in anti-wrinkle- and eye preparations. The latter mentioned work well for the treatment of the dry eye syndrome which develops in particular with VDU work, low room humidity and deficient lacrimation – symptoms are redness and inflammations. Appropriate solutions of hyaluronic acid compounded with phosphatidylcholine liposomes are simply sprayed onto the closed eye. Dry and possibly inflamed nasal mucous membranes are a similar example of application; a compound of hyaluronic acid and

D-panthenol is sprayed into the nose, preferably in the evening before going to bed.

Radical scavenger and antioxidant

Similar to many other polysaccharides, hyaluronic acid is an excellent radical scavenger on the skin surface. Thus it also provides a slight protection against the UV radiation of the sun. This protection is not achieved by absorbing the sun radiation as with UV filters but by reaction of the radiation-induced oxygen radicals with the sugar structures which renders them harmless. In addition to it, the ubiquitous heavy metals, as e.g. iron, that participate in the radical formation, are neutralized through complexation. Similar experience has been gained with CM-glucan which is another polysaccharide used in the cosmetic field.

The antioxidant effect of the concentrations used in skin care preparations is limited though. Doses of 0.1%-0.2% in the dry matter considerably improve the consistency of gels, a fact which is due to the high water retention capacity of hyaluronic acid. Even if advertising messages frequently speak of a 10% or even higher content: a closer look often reveals that these numbers turn out to be the gel concentrations in the finished product. The concentration of 1% of hyaluronic acid in the 10% of aqueous gel contained in the finished product results in the above mentioned real concentration of 0.1%.

Cross-linked hyaluronic acid

Hyaluronic acid is easily degraded, as already mentioned above. This process is not only due to the activity of microorganisms but also due to the natural hyaluronidases of the body that affect the fillers used for anti-wrinkle injections. In other words, the effect of fillers would be very short-lived when using body-identical hyaluronic acid. That is why the cosmetic industry today usually works with modified hyaluronic acids that are largely resistant to hyaluronidase. The modification of natural hyaluronic acid is a chemical process in which the hyaluronic acid chains are cross-linked.

The links are built up at the hydroxyl-, carboxyl- and/or deacetylated amino groups of the molecule through condensation with poly-functional alcohols, aldehydes, carboxylic acids, epoxides and several other chemicals. Since the water-retaining capacity inevitably is impaired by cross-linkage processes, some expertise is required to find an adequate compromise between water retention, resistance to degradation and tolerability. Cross-linkage mechanisms certainly do not matter in the context of topical preparations.

Additional polysaccharides

Hyaluronic acid retains water, has film-forming features and influences the consistency of skin care preparations. Many polysaccharides and derivatives of cellulose and starch have similar properties⁸ but usually do not have the excellent water retaining capacity and hence easily dehydrate. In higher concentrations the thus related evaporation causes a surface film that can be removed, comparable to parchment.

Food supplements

Beauty care from inside out is in vogue and there are all kinds of different food supplements on the market. Hyaluronic acid is no exception in this context. It should however be mentioned that the European Food Safety Authority (EFSA) does not rate respective claims as for instance “preserving young skin” or “excellent skin hydration” as scientifically proven even if a Japanese study has been carried out and allegedly supports the claims.⁹ According to the directive (EU) No. 1066/2013, issued by the commission on 30 October 2013, on “refusing to authorize certain health claims made on foods, other than those referring to the reduction of disease risk and to children’s development and health”, such kind of claims are not allowed – if they are not explicitly authorized (“reservation of authorization”). The advertising texts for respective capsules thus evade the issue by speaking of hyaluronic acid deficits which settle in with the aging process of the skin. A parallel can be drawn between the descriptions of hyaluronic acid- and oral collagen preparations.¹⁰

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⁸ Lautenschläger H, (Poly)Saccharide in Kosmetika – Von A wie Alginat bis Z wie Zuckertensid, Kosmetische Praxis 2009 (4):12-15

⁹ <https://www.verbraucherzentrale.de/wissen/projekt-klartext-nem/ist-hyaluronsaeure-gut-fuerhaut-und-gelenke-28509>(Download 1.11.2018)

¹⁰ Lautenschläger H, Studien in der Kosmetik – Was ist wahr?, medical Beauty Forum 2018 (3):14-18