Hyaluronic Acid: Is It Effective?

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Hyaluronic acid (HA) is a large linear polysaccharide known as a glycosaminoglycan, composed of repeating amino-disaccharide units. Like other glycosaminoglycans, it is found in connective tissues and organs throughout the body, where its complex shape and hydrophilic nature make it an important contributor to structure, hydration, viscosity, and lubrication. The first medical use for HA was as vitreous replacement during eye surgery; more recently, its use has expanded to include treating osteoarthritis, promoting wound healing, and cosmetic purposes. Because it generally occurs at a molecular weight believed to exceed the absorptive capacity of the small intestine, HA has mainly been used in injectable form.[i] [ii] More recently, oral preparations have become popular, raising the question: Does it work? And, if so, how?

Clinical Evidence

Despite its large molecular size, findings from clinical trials show that oral HA can reduce pain related to osteoarthritis. In fact, oral supplements (300 mg daily of HA plus 100 mg of *Boswellia serrata* for 20 days, followed by 150 mg daily of HA alone for 20 days) were found in one trial to be as effective as intra-articular injections (1.6% HA, three times weekly) in relieving knee osteoarthritis pain, and appeared to be more effective than injections in a subgroup of older subjects.[iii] In one placebo-controlled trial with 78 participants, 225 mg of HA was more effective than placebo for relieving knee pain due to osteoarthritis after two weeks. Along with reduced pain, those receiving HA also had improved sleep and used less pain medication at the end of four weeks.[iv] In a 12-month trial, 60 participants with osteoarthritis of the knee were assigned to perform daily quadriceps strengthening exercises and take either 200 mg HA per day or placebo; among participants aged 70 and younger, taking HA was associated with greater osteoarthritis symptom relief compared with placebo.[v]

Positive effects of HA on skin have also been reported. A double-blind placebo-controlled trial in 60 male and female subjects found that those receiving 120 mg per day of HA for 12 weeks had diminished skin wrinkles and improved skin condition.[vi] In a preliminary study, increased skin hydration and elasticity and decreased skin roughness and wrinkles were measured in 20 healthy middle-aged women who had taken a supplement containing HA, biotin, vitamin C, zinc, and copper for 40 days. (Unfortunately, the study authors did not disclose the doses of the supplement ingredients.)[vii] In addition, results from several trials involving the use of 100–240 mg per day of oral HA indicate its ability to relieve dry skin.[viii]

Other large structural polysaccharides may also be useful as oral supplements for connective tissue health. Despite widespread doubt regarding its bioavailability, the glycosaminoglycan chondroitin sulfate has demonstrated consistent clinical benefits and is widely used as a treatment for osteoarthritis in a variety of joints.[ix] Researchers investigating the effects of an eggshell membrane extract rich in glycosaminoglycans, including HA, recruited female volunteers for a pilot trial. The women experienced enhanced skin quality after taking 300 mg daily of the eggshell membrane extract for 50 days. The same report described another pilot trial in which objective measures of skin quality, such as elasticity and pigmentation, were improved after 35 days of supplementation.[x] In a 60-day, double-blind, placebo-controlled trial in 67 participants with osteoarthritis of the knee, those receiving 500 mg per day of eggshell membrane extract had reduced arthritis pain and stiffness after ten days compared with placebo, and this pain reduction persisted through the end of the trial.[xi]

Hyaluronic Acid Absorption and Accumulation

A pharmacokinetic study in rats found that orally administered HA was likely decomposed by intestinal bacteria into di-, tetra-, and polysaccharides that were then absorbed through the small intestinal wall and distributed into tissues such as skin.[xii] Another study in rats reported a 90% absorption rate for oral HA,

and with the use of radioactive labeling, showed that it traveled through the bloodstream and was deposited, in varying amounts, in all of the tissues examined.[xiii] Research in rats and dogs using a radiolabeled oral HA also noted its deposition in joints and other tissues after ingestion,[xiv] providing further evidence in favor of absorption.

Nevertheless, pharmacokinetic trials in humans confirming its absorption and accumulation in tissues are still needed. In fact, there is evidence that some of the clinical benefits seen with oral HA may be independent of absorption: In animal research, HA was found to interact with toll-like receptor-4 on intestinal epithelia (cells that line the inner intestine), triggering increased production of the anti-inflammatory cytokine IL-10, as well as epigenetic alterations associated with reduced inflammatory potential.[xv] [xvi]

Importance of the Gut Microbiota

The micro-organisms that colonize the intestines are likely to impact the activities of all compounds passing through the digestive tract. There is growing evidence that many phytochemicals, including such important compounds as polyphenols and isoflavones—well known for their low oral absorption, exert their benefits at least partly through interactions with the gut microbes.[xvii] [xviii] Even widely used medications such as prednisolone, ranitidine, and metformin appear to undergo some microbial metabolism affecting their activities.[xix] [xx] It may therefore not be surprising that gut microbes appear to play an essential role in the bioavailability and activity of HA.

Early microbiological research has demonstrated that some bacterial species normally found in the human gut can ferment HA,[xxi] possibly yielding bioavailable HA oligosaccharides. An *in vitro* model of human intestinal absorption found that the degree of absorption of HA oligosaccharides was inversely dependent on their size and molecular weight: as polymer size decreased, absorption increased,[xxii] highlighting the potential importance of intestinal microbial digestion to HA bioavailability.

Breaking it Down

If the gut microbiota is indeed crucial to the effectiveness of oral HA, there may be inter-individual differences in its health benefits based on gut health and microbiome composition. Hydrolyzed HA and other glycosaminoglycans are available and may reduce the impact of this variable. In a pilot study, an oral supplement containing hydrolyzed HA and collagen, as well as vitamins and minerals, was given to healthy subjects; after 60 days, improvements in skin dryness, firmness, and wrinkles were reported.[xxiii] Similarly, taking 1 gram daily of hydrolyzed cartilage containing oligosaccharides of HA, collagen, and chondroitin sulfate for 12 weeks was reported to reduce visible dryness and wrinkles in healthy women with signs of photoaging.[xxiv] While this early evidence suggests some efficacy, it is not yet known whether hydrolyzed glycosaminoglycans have any advantages over their un-hydrolyzed counterparts.

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