7 Hyaluronic Acid in Modern Cosmetic and Reconstructive Surgery

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7.1 Introduction

Hyaluronic acid (HA) is a ubiquitous substance that is found in connective tissues, joints, muscles and in the skin. It is an essential glycosaminoglycan that acts as a network to transfer essential nutrients from the bloodstream to cells. Modern plastic surgery employs various synthetic forms of HA to improve skin aesthetics, to correct joint pathologies and to reconstruct the skin after injury. This chapter outlines some of the important aspects of HA and its implementation in modern reconstructive surgery.

7.1.1 Reconstructive and Aesthetic Surgery

Plastic surgery is a medical specialty that focuses on the aesthetic and functional reconstruction of various parts of the body, including skin, the musculoskeletal system, craniomaxillofacial structures, extremities, breast, trunk and external genitalia [1]. Recent innovations in materials science and surgical techniques have enabled surgeons to perform microvascular procedures, craniomaxillofacial surgeries, liposuction, tissue transfer and to use dermal fillers [1]. Within this chapter, we discuss the implementation of HA in reconstructive procedures for modern plastic surgery.

7.1.2 Modern Reconstructive and Aesthetic Plastic Surgery

Reconstructive surgery aims to improve the function and appearance

of abnormalities secondary to congenital defects, trauma, malignancies or burns [2].

Aesthetic, or cosmetic, surgery, on the other hand, is performed to improve a patient's appearance using invasive or non-invasive procedures. Invasive procedures are used, for example, to give a more youthful appearance to the face or body, or to remove excess skin after pregnancy, or significant weight loss. Non-invasive techniques are used, for example, to treat pathologies of the skin, including wrinkles, scars, pigmented spots, tattoos, and telangiectasias. The most common non-invasive procedures performed to date include botulinum toxin, filler injections, chemical peels, cosmetics, lasers, and mesotherapy [1]. According to the statistics of the American Society for Aesthetic Plastic Surgery (ASAPS), there was a 10% increase in non-surgical procedures in 2012. HA injections were the second most popular treatment among them.

7.2 Hyaluronic Acid

HA was first described by Karl Meyer, the father of glycosaminoglycan (GAG) chemistry [2]. It was further developed by Endre Balazs who established methods to produce and apply the molecule in medicine [3].

It is one of the major elements of the connective tissue in both human and mammals, and it is present in the extracellular matrix (ECM) of the skin and muscles, and in high concentrations in the vitreous body of the eye, and in the joints [4]. In the skin, its main function is conservation of volume and tone. It gradually diminishes with age, leading to the progressive formation of wrinkles and skin imperfections.

Chemically, HA is an anionic, unsulfated GAG. Its main component is a non-branched chain polysaccharide composed of thousands of disaccharide units, residues of glucuronic acid and *N*-acetylglucosamine [5]. *In vivo*, all carboxylic groups of the

glucoronic acid are ionised, providing molecular polarisation, hydrophilicity and increased solubility in water (**Figure 7.1**). Due to its polar nature, it provides increased hydration and moisturisation in the matrix of the skin (dermis). It can bind to water molecules and increase its weight by 1,000 times and its volume by 18-20 times. Its hydrophilic nature acts as cell lubricant, decreasing the damage caused by friction between cells [6].

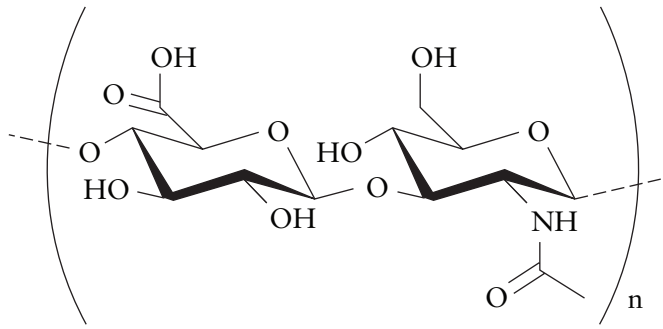

Figure 7.1 The repeat unit of HA

The half-life of HA ranges from 12-24 ~~h~~ days in both the dermis and the epidermis. The presence of HA in epithelial tissues promotes keratinocyte proliferation and increases the presence of retinoic acid, causing skin hydration. HA interaction with CD44 antigen drives collagen synthesis and normal skin function. Present in the ECM of basal keratinocytes, HA is critical to the structural integrity of the dermal collagen matrix.

HA is isolated either from animal (bovine/porcine) or non-animal (bacterial) sources. The majority of the HA fillers used in aesthetic plastic surgery are non-animal derived, mainly made by bacterial fermentation or chemically synthesised and further crosslinked to improve biocompatibility and mechanical properties.

7.2.1 Application of Hyaluronic Acid in Reconstructive Surgery

Over the past two decades, HA has become the most extensively used material in plastic surgery, ophthalmology and orthopaedics. The use of HA in reconstructive surgery, as a dermal filler, dressing, or cream, centres on the restoration of soft tissue defects, and the treatment of wounds and burns. Typically, these defects are secondary to surgical or physical trauma, especially in subtractive surgeries, such as tumour removal. HA is used as a filler due to its ability not only to restore the lost volume, but to also improve the quality of the skin, namely its elasticity, plasticity and hydration.

HA dressing or cream is also frequently applied in the treatment of chronic wounds and burns. Chronic wounds originate from skin lesions that remain unresolved for more than three months [7]. The healing process involves several complex and dynamic changes, such as: haemostasis, inflammation, proliferation and remodelling of dermal tissue [8]. The participation of biological factors, such as cytokines, chemokines, growth factors, components of the extracellular space, proteases and cell receptors, is vital for the normal healing process [9]. However, prolonging the healing process and overexposure to proinflammatory cytokines can abrogate the restoration of normal tissue, especially in the proliferative phase where granulomatous tissue is formed by HA, fibronectin, collagen and GAG. During healing, HA helps with tissue neovascularisation and establishes the necessary microenvironment to promote migration of fibroblasts, endothelial cells and keratinocytes and increase the levels of growth factors [10].

Skin exposure to excessive heat, chemicals, radiation, electric current, or even mechanical friction results in burns and skin lysis due to damage to the underlying tissues. The severity of the burn depends on its depth and is classified according to degrees. First degree burns are superficial and do not result in scarring. Second degree burns, are further classified as Type-A, with complete aesthetic restoration and Type-B that do not necessitate any surgical intervention, but

will result in some skin discoloration after healing. Third and fourth degree burns involve the full thickness of the skin and require reconstructive surgery to remove scarred tissue or repair disfiguration of the face or body. Mosaic burns include different degrees of depth [11]. HA provides increased hydration, activates neocollagenesis and neoangiogenesis and as a result, it is widely used to treat first and second degree burns with excellent aesthetic results either as a dressing or a cream. The benzyl esters of HA have been studied thoroughly as HA derivatives [12, 13].

7.2.2 Hyaluronic Acid as a Filler and Skin Biorevitaliser

Facial characteristics are defined by the skin, muscles and bones. Over the years, the face loses its youthful appearance. Body weight, hormonal changes, ultraviolet radiation, smoking and gravity lead to the appearance of depressions and wrinkles. In addition, the loss of the skin's elasticity becomes apparent after the age of 30. Areas of the face most affected are: the periorbital, malar, forehead, temporal, glabellar, mandibular, mental and perioral zones [14-16].

HA injections can restore the natural and youthful appearance of the skin. This minimally invasive procedure restores tissue volume, reduces wrinkles and fills the depressed areas by local absorption. The use of HA as a skin filler became popular in the mid-1980s and, according to the ASAPS, it is considered to be the fastest growing, non-invasive, procedure in the United States [17]. Filler HA is a viscous, transparent gel, which can be injected through a small gauge (G) needle, typically of 23-27 G. It provides increased volume and skin hydration due to its hydrophilic nature. Deep wrinkles require a high concentration of HA (approximately 25 mg/ml), while shallow wrinkles are typically treated with a lower concentration (5 mg/ml). HA filler lasts approximately 8-16 months in the skin, depending on the age, the type of skin, the muscle activity of the underlying tissue, the depth of the injection, and the density of the material.

There are other absorbable fillers, such as collagen (bovine- or porcine-derived) injections, calcium hydroxyapatite (biodegradeable microparticles), poly(L-lactic acid) (PLLA) and non-absorbable fillers such as Artefill (polymethyl methacrylate (PMMA) with collagen) and silicone injections. **Table 7.1** lists the most popular dermal fillers available in the United States [18]. Compared to the above-mentioned fillers, HA has the safest biological profile, and it is fully absorbable and biodegradable [19]. Crosslinking of its macromolecular chains increases its resistance to degradation by matrix metalloproteinases and extends its life in the body [6].

Non-crosslinked HA may also be used for skin biorevitalisation, a process of inducing fibroblast stimulation and regeneration of the intracellular components that support the dermis Biorevitalisation with HA is different from applications of HA as a filler. Although both procedures provide a reduction in skin wrinkles and folds biorevitalisation can also provide skin rehydration, treat skin irritation, reduce muscle tone of the face and neck, correct skin sagging of the abdomen, inner thighs and upper arms, reduce wrinkles around the eyes, chest and upper lip, as well as remove the dark circles around the eyes and shrink enlarged oily skin pores. This treatment provides reduction in skin wrinkles and dermal folds and is used for skin preparation prior to chemical peels or laser treatments [20-26].

Table 7.1 Most popular dermal fillers available in the USA

Active components	Non-absorbable	Absorbable synthetic		Absorbable natural			
	PMMA	Calcium hydroxapatite microspheres	PLLA	Bovine collagen	Human collagen	Porcine collagen	HA
Brand name (manufacturer)	Artefill (Artes Medical)	Radiesse (BioForm Medical)	Sculptra (Sanofi-Aventis)	• Zyderm (Allergan) • Zyplast (Allergan)	• Cosmoderm (Allergan) • Cosmoplast (Allergan)	Evolence (ColBar Life Science)	• Restylane (Medicis Aesthetics) • Perlane (Medicis Aesthetics) • Juvederm (Allergan) • Prevelle Silk (Genzyme Biosurgery) • Elevess (Anika Therapeutics)

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7.2.3 Complications

All surgical procedures, even non-invasive ones, involve risks and complications. The most common adverse effects of HA injection are pain, induration, itching, swelling, redness and inflammation around the injection site. These adverse effects may resolve within a few days without intervention [27]. Another less common complication, known as the Tyndall effect, is a dark shadowing under the skin, caused by superficial injection of HA or nodule formation. Rare complications include allergic reaction, hypersensitivity and biofilm formation around the HA. Granulomatous reaction can also occur around the HA. However, these are typically invisible, although they remain palpable [6]. Noticeable granulomas can be treated with corticosteroid injections. The most severe complications of HA application, although very rare, are skin necrosis and blindness, caused by compression or occlusion of a blood vessel [28, 29].

Biorevitalisation with HA is also considered to be a safe procedure with limited side effects, mostly associated with temporary swelling and redness of the skin. Rare complications may include inflammatory reaction and infection.

7.3 Overview

In addition to the many applications of HA in materials science and chemistry, plastic surgery has extensively adopted the use HA in everyday standard aesthetic treatments. Its excellent hydrophilicity and biocompatibility makes this molecule a safe and attractive agent in aesthetic and reconstructive surgery.

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