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Hyaluronic acid in skin and oral mucosa wound healing

A Project Submitted to
The College of Dentistry, University of Mosul, Department of Basic Sciences in Partial Fulfillment for the Bachelor of Dental Surgery

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Certification of the Supervisor

I certify that this project entitled " **Hyaluronic acid in wound healing** " was prepared by the fifth-year student **Ahmed Hasan**

under my supervision at the College of Dentistry/University of Mosul in partial fulfillment of the graduation requirements for the Bachelor Degree in Dentistry.

Supervisor's name: **Prof. Dr. Faehaa Azher**

Date:5\3\2025

Dedication

As well as everything that I do, I would be honored to dedicate this project to my parents and my brother. They supported me and encouraged me on every step in my life and they gave me everything necessary to be who I am now. Finally, my dream came true, and I am writing my graduation project from the College of Dentistry / University of Mosul. Last but not least I would like to thank my supervisor **Faehaa Azher** to help me in this project and I am very lucky to be under her supervision.

Acknowledgments

First and foremost, praise and thanks to Allah Almighty for helping me fulfill my dream, for His blessings throughout my work to complete it successfully. I would like to extend my deepest respect and gratitude to the Dean of the College of Dentistry, University of Mosul. I would like to show my deep and sincere gratitude to my research supervisor, **Dr. faehaa Azher**, for her advice, encouragement, and guidance in planning and conducting this project.

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INTRODUCTION

The skin and oral mucosa act as a barrier against physical and microbial insults, also a protective layer to the outside environment. They consist of similar layers and share the same features such as a stratified squamous epithelium covering. A wound is defined as a break in the continuity of the covering skin, and/or lining mucosa. Generally speaking, wounds can be classified into acute or chronic wounds, depending on the depth of tissue at the injury site and the period of healing as in pressure ulcers. Another classification is based on the level of bacterial contamination. Regarding wound closure (how the wound heals) it can be classified into a primary, secondary, or tertiary intention. The wound healing process is a complex mechanism involving a cascade of coordinated inflammatory and proliferative steps. Different biomaterials might be required to improve clinical outcomes, and have a potential function in wound healing and regeneration, thereby playing an important role in tissue repairing mechanisms in many oral surgical procedures. **(Armitage J., and LockwoodS., 2011; Tejiram S., et al., 2016).**

Hyaluronic acid is a polysaccharide of the extracellular matrix of connective tissue, it consists of repeated disaccharide units of D-glucuronic acid and N-acetyl glucosamine. The biological action of Hyaluronic acid comes from its relation to osmosis (anti-edematous effect), a potential function with growth factors, and lubricant for various body tissues. Thus maintains the structural integrity of the tissue. Properties of Hyaluronic Acid include; The biocompatibility, non-immunogenicity with viscoelastic nature make it unique to be used in several applications as in facilitating scar-less healing and regeneration of incision wounds, reducing the penetration of viruses/bacteria into the tissue, and regulating the inflammatory reaction**. (Liu Z. et al., 2008; Casale M., et al., 2016).**

AIMS OF STUDY

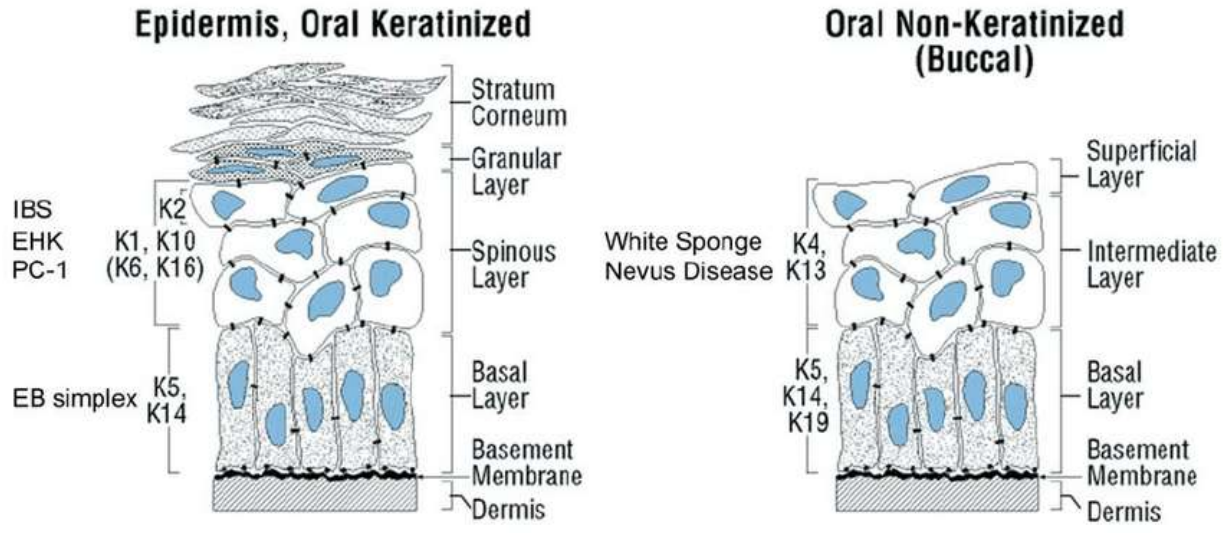
The aim of this study was to review the role of hyaluronic acid in modulating the wound healing process for both skin and oral mucosa.

CHAPTER ONE

REVIEW OF LITERATURE

1.1 Anatomy of Skin and Oral Mucosa

The skin and oral mucosa act as a protective barrier to the outside environment. They both contain structurally similar layers and share similar features. The outer layer of skin and oral mucosa is covered with stratified squamous epithelium, providing a barrier against physical and microbial insults. (**Qin R., et al., 2017**). Oral mucosa consists of two layers, the covering epithelium, and the underlying connective tissue layer, the lamina propria. Nomenclature differs between the skin and oral mucosa, such as the dermis of the skin is equivalent to the lamina propria of the mucosa. (**Evans EW., 2017**). The histologic differences between keratinizing, non-keratinizing mucosa, and skin may be summarized in Figure (1.1).



The epidermis, oral mucosa, keratinized. Oral mucosa, non-keratinized.

Figure (1-1): Differences between keratinizing, non-keratinizing mucosa and skin (**Presland RB., Jurevic RJ. 2002**).

1.1.a The Skin

The integumentary system consists of the skin and the appendages, its derivative structures, including hair follicles, nails, sebaceous, and sweat glands. Three distinct layers of the skin: the epidermis, the dermis, and the hypodermis. (**Y. Gilaberte, et al., 2016**).

1.1.a.1 The Epidermis

The epidermis is the most external layer of the skin, formed by a stratified squamous epithelium, and is composed basically of keratinocytes (the most predominant cell type). The epidermis is divided into four layers, resting on the basement membrane is the basal layer, the stratum spinosum or prickle cell layer, the next outer layer; the granular cell layer (stratum granulosum) is the last stratum that contains living cells, the keratinocytes suffer a transformation into flat, anucleated cells, the stratum corneum (the most superficial layer of the skin). The epidermis can replace dying cells and maintain the tissue barrier against harmful pathogens and retains vital body fluids. (**Presland RB., Jurevic RJ. 2002**).

1.1.a.2 The dermis

A thick layer of fibrous and elastic tissue provides structural and nutritional support to the epidermis. The dermis is composed of a mucopolysaccharide held together by collagen (giving it strength and toughness), and elastic (maintains normal elasticity and flexibility) fibers. Blood and lymphatics, nerves, sweat, and sebaceous glands, hair roots, are embedded within the fibrous tissue of the dermis. (**Y. Gilaberte, et al., 2016**).

1.1.a.3 The hypodermis

The hypodermis is predominantly formed by adipocytes, which are organized into lobules separated by fibrous tissue The hypodermis serves as a reservoir for energy supply, protecting the skin, and allows mobility over underlying structures. (**Presland RB., Jurevic RJ. 2002; Y. Gilaberte, et al., 2016**).

1.1.b Oral mucosa

Oral mucosa is the moist lining of the oral cavity. It mainly consists of stratified squamous epithelium and underlying lamina propria, areas of cheeks, lips, and parts of the hard palate, a layer of loose fatty connective tissue containing the major blood vasculature and nerves called the submucosa that separates the mucosa from underlying bone or muscle. (**Hassona Y., and Scully C., 2013**). The mucosa is divided into three types: masticatory, lining, and specialized mucosa (**Squier C., and Brogden K.2011**).

1.1.b.1 Masticatory Mucosa

The epithelium is moderately thick and covers those areas of immobile structures (the hard palate and gingiva), which are exposed to abrasion due to mastication of food and to compressive and shear forces. Histologically, it is frequently ortho-keratinized although there are para-keratinized areas of the gingiva of the palate. The submucosa is a very thin layer or somewhat absent, this will increase the firmness of the tissue. The lamina propria is thick, containing dense closely packed bundles of collagen fibers, enabling the mucosa to resist heavy loading. (**Yaman D., et al., 2014; Valach J. et al., 2017**).

1.1.b.2 Lining Mucosa

It forms about 60% of the total surface area, covering the underside of the tongue, inside of lips, the floor of the mouth, and cheeks, together with the soft palate. All these areas are covered by thick non-keratinized epithelium. (**Wanasathop A., and Li SK. 2018; Groeger S., and Meyle J., 2019**). The connection between epithelium and lamina propria is somewhat regular, and projections of connective tissue known as the papillae, interdigitate with epithelial rete-pegs (**Sa G., et al., 2012**). The lamina propria is thicker than in masticatory mucosa and contains fewer collagen fibers, associated with elastic fibers Thus, the mucosa can be stretched to an extent before these fibers limit further distention. With a loose elastic submucosa, the tendency for lining mucosa to be flexible means that surgical incisions require suturing for closure (**Squier C., and Brogden K., 2011**).

1.1.b.3 Specialized Mucosa

Unlike anywhere else in the oral cavity, usually found on the dorsal and lateral surface of the tongue, and has different types of lingual papillae: fungiform and filiform papillae found in the anterior portion of the tongue, the Foliate papillae present on the lateral margin of the tongue, anterior to the sulcus terminalis are the circumvallate papillae. Lingual papillae bear taste buds and therefore have a special sensory function, others possess a mechanical function. (**Squier C., and Brogden K., 2011; Qin R., et al., 2017**).

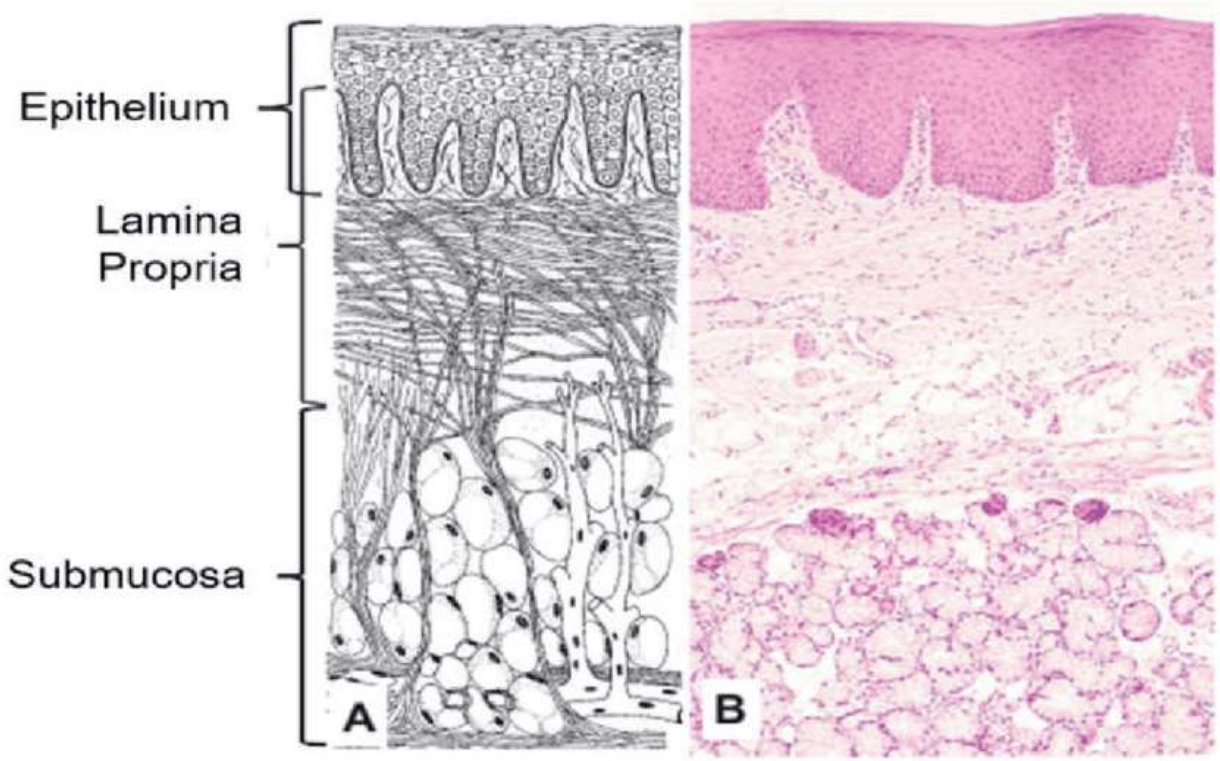


Figure (1-2): Main tissue components of the oral mucosa. (**Cruchley A.T.,2018**).

1.2 Wound: Definition and Classification

A wound can be defined as a break in the integrity of the covering skin,lining mucosa, or injury to other body tissues (**Kang MH and Kim BH 2018**).Wounds can be categorized into either acute or chronic, based on the period of healing (within six weeks regarded as acute). (**Tejiram S., et al.,2016**).

Other classification based on the level of bacterial contamination (operative wounds): clean, clean-contaminated, contaminated, and dirty. Regarding wound closure. It can also be classified into primary intention, secondary intention, and tertiary intention (delayed primary closure). (**Dumas SE., et al., 2016; Tejiram S., et al., 2016**).

1.2.a Wound Classification Based On the Period of Healing

1.2.a.1 acute wound

Any accidental or surgical wound that heals completely by primary or secondary intention by the phases of normal healing in a short period (within six weeks). (**Tejiram S., et al., 2016**).

1.2.a.2 chronic wound

The presence of skin and/or mucosal defect or lesion that persists more than six weeks, or has a tendency to recur, so healing is postponed and becomes trapped in the inflammatory phase affected by many factors; poor nutrition medications or inappropriate dressing of the wound. (**Young A., McNaught C-E. 2011**).

1.2.b Classification of Surgical Incision (Operative) Wounds:

Dumas SE., et al., (2016).

I. Clean wound, the surgical site is not inflamed or contaminated, and naturally colonized with micro-organisms,

II. Clean-contaminated, operative wounds in which system tracts are entered under controlled conditions.

III. Contaminated, includes open traumatic wounds (open fractures and penetrating wounds).

IV. Dirty or infected wounds, active infection at the surgical site.

1.3 Wound Healing

It is a complex process involving a coordinated sequence of events required to restore normal tissue layers, it can be divided into four phases; Haemostasis, the inflammatory phase, a proliferative, and the remodeling phase. (**Armitage J., and Lockwood S., 2011**).

1.3.a Phases of Wound Healing

Phase I: Haemostasis

Begins with the activation of platelets, that initiate the coagulation cascade, and influence wound healing, substances that released by platelets include; platelet-derived growth factor (PDGF), the transforming growth factors (TGFs), the fibroblast growth factors (FGFs), and vascular endothelial growth factor (VEGF). (**Shah JM., 2012**).

Phase II: Inflammation

Tissue injury causes blood vessel disruption with concomitant extravasation of blood. coagulation of blood and platelet aggregation generate a fibrin clot that occludes severed vessels and fills any discontinuity in the area of wounded tissue. the clot within the wound space acts as a growth factor reservoir, providing a provisional matrix for cell migration. (**Eming SA., 2014**).

Phase III: Proliferation

Proliferation consists of three distinct phases; fibroplasia, granulation, and epithelialization, it begins with the migration of fibroblast into the wound, initiated by the PDGF which is released by platelets and macrophages, and in turn, stimulates fibroblastic proliferation, and chemotaxis. Angiogenesis replaces

damaged blood vessels with granulation tissue. Fibroblasts, vascular endothelial cells, contribute to angiogenesis by the production of VEGF. Tissue hypoxia stimulates VEGF-induced angiogenesis. Re-epithelialization begins with the proliferation and migration of the epithelial cells, helped by epidermal growth factors (EGFs), and keratinocyte growth factors (KGFs). The cells interact closely with the extracellular matrix and continuously stimulating each other. (**Shah JM., et al., 2012**).

Phase IV: Tissue Remodeling

Remodeling or resolution stage, the final step in wound repair, Fibroblasts continue to lay down collagen, and they begin to decrease in number, crosslinking of collagen molecules takes place, the number of cells that release the growth factors become fewer. the tensile strength of a healed wound is higher than that possessed by normal tissue by 80%. (**Eming SA., 2014, Shah JM., 2012**).

Type III collagen is remodeled into type I, and the early inflammation will be degraded (**Gonzalez AC., et al., 2016**).

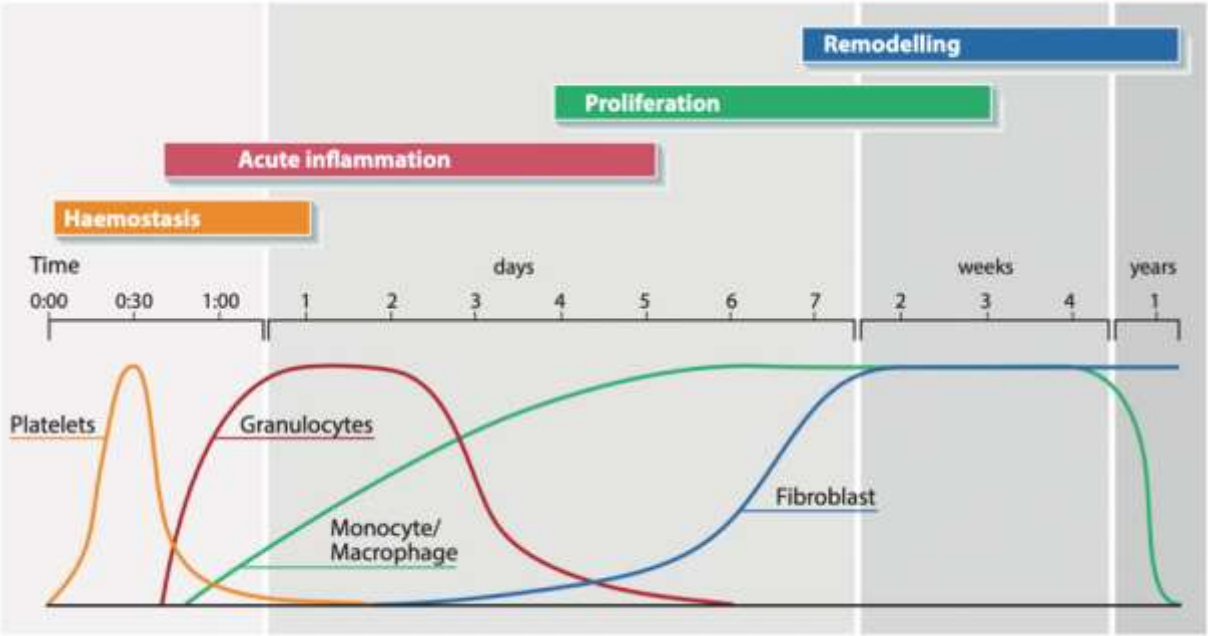


Figure (1-3): The phases of wound healing. (**Sharma MV., 2018**).

1.3.b Types of Wounds Healing

1.3.b.1 Healing by (First) Primary Intention

If the wound margins can be gathered or re-approximated, so the wound is said to be healed by primary intention, tissue repair takes place by the creation of tissue granulation and re-epithelialization with little or no sign of scar tissue. such wounds can be created in an aseptic environment (minimal bacterial contamination) and minor tissue damage. (**Mickelson MA., et al., 2016; Kirwan H., and Pignataro R. 2016**).

1.3.b.2 Healing by Secondary Intention

When it is difficult to approximate the wound edges, so the wound is healed by secondary intention, healing occurs when wounds are characterized by a significant tissue loss, as seen in major trauma, burns, infection, and after some surgical

procedures as in excisional biopsy taking. Healing takes place by granulation tissue formation and subsequent contraction of the wound. because a large gap is formed (in huge defects), such a wound is left open, resulting in the formation of scar tissue. (**Armitage J., and Lockwood S., 2011; Kirwan H., and Pignataro R., 2016**).

1.3.b.3 Healing by Tertiary Intention (Delayed Primary Closure).

If the wound edges are intentionally left open days after surgery or injury. These wounds include; necrotic and infected wounds, traumatic wounds, or those caused by animal bites or projectiles. Such wounds need a thorough toilet before the closure is accomplished. (**Siribumrungwong B., et al., 2014, Kirwan H., and Pignataro R., 2016**).

1.3.c Factors Affecting Wound Healing Process.

1.3.c.1 Local Factors:

1.3.c.1.a Tissue Oxygenation and Blood Supply.

Oxygen is necessary for survival and, cell metabolism, therefore healing. Energy production in the form of Adenosine triphosphate (ATP), in the presence of oxygen(O2), is critical for all wound healing processes, preventing infection, inducing angiogenesis, increasing differentiation, migration, and re-epithelialization, of keratinocytes, enhancing fibroblast proliferation and synthesis of collagen, thus promotes wound contraction. (**Guo S., and Dipietro LA., 2010**).

1.3.c.1.b Infection of the Wound.

Once the tissue is injured, microbial flora that are normally present at the skin or mucosal surface obtain access to the underlying tissues. The wound is classified

according to the state of infection and replication status as having: contaminating, critically colonizing, and spreading or invading infection. (**Guo S., and Dipietro LA., 2010**).

1.3.c.2 General factors:

1.3.c.2.1 Ageing

As a person ages, healing potential will be more slowly than that in younger patients. A reduction in tissue metabolism means tissues lose their tone and elasticity, this will lead to a decline in the healing process. Aging causes many changes in the tissues and underlying structures rendering the individual more liable to injury and less be able to efficiently heal. (**Bonifant H., and Holloway S., 2019; Guo S., and Dipietro LA., 2010**).

1.3.c.2.2 Nutritional Status

For a wound to heal, it requires Adequate nutrition, and this can be accomplished by the presence of trace elements and vitamins. The absence of these elements can negatively affect the synthesis and transport of growth factors, cytokines, and enzymes, thus affects wound healing potential. (**Anderson K., and Hamm RL., 2014**).

1.3.c.2.3 Stress

Psychological stress leads to Enhanced glucocorticoids and catecholamines Production, this will result in decreased neutrophils infiltration, pro-inflammatory cytokines, and increased wound hypoxia. All these factors can negatively modulate the healing response and impair wound healing. (**Gouin JP., and Kiecolt-Glaser JK. 2011**).

1.3.c.2.4 Medications

Medications that interfere with platelet aggregation, clot formation, and inflammatory responses, have the effect to impair wound healing. Other medications like Chemotherapeutic agents well-known to impair or stop rapidly proliferating or growing cells including those involved in the healing of such a wound. (**Guo S., and Dipietro LA., 2010**).

1.4 Surgical Incisions

When the skin or soft tissue is intentionally cut or wounded to facilitate an operation or procedure. Every incision must be performed by the surgeon, considering the therapeutic, functional, and aesthetic results of scar formation. The key principles of surgical incisions are; they should provide maximum wound strength with minimal scarring, and wherever possible muscles should be split and not cut. (**Schmidt K., and Ziegler UE. 2004**).

1.7 Hyaluronic acid (HA)

Hyaluronic acid is a naturally occurring polysaccharide of the extracellular matrix of connective tissue. The structure of HA consists of repeated disaccharide units of D-glucuronic acid and N-acetyl glucosamine linked by glycosidic bonds. It presents in the extracellular matrix of synovial fluid, skin, and many other tissues of the body. The unique characteristics of HA among other glycosaminoglycans; it is non-sulfated, formed in the plasma membrane rather than the Golgi apparatus, and possesses a high molecular weight. The biological action of HA comes from its relation to the osmotic pressure (anti-edematous properties), a potential role with growth factors, and tissue lubrication. All these functions help maintain the structural integrity of the tissue. It is synthesized in the cell membrane by a membranebound protein by most cells of the body and directly secreted into the

extracellular space, in the presence of endotoxins it is mainly released by fibroblasts. (**Casale M., et al., 2016**).

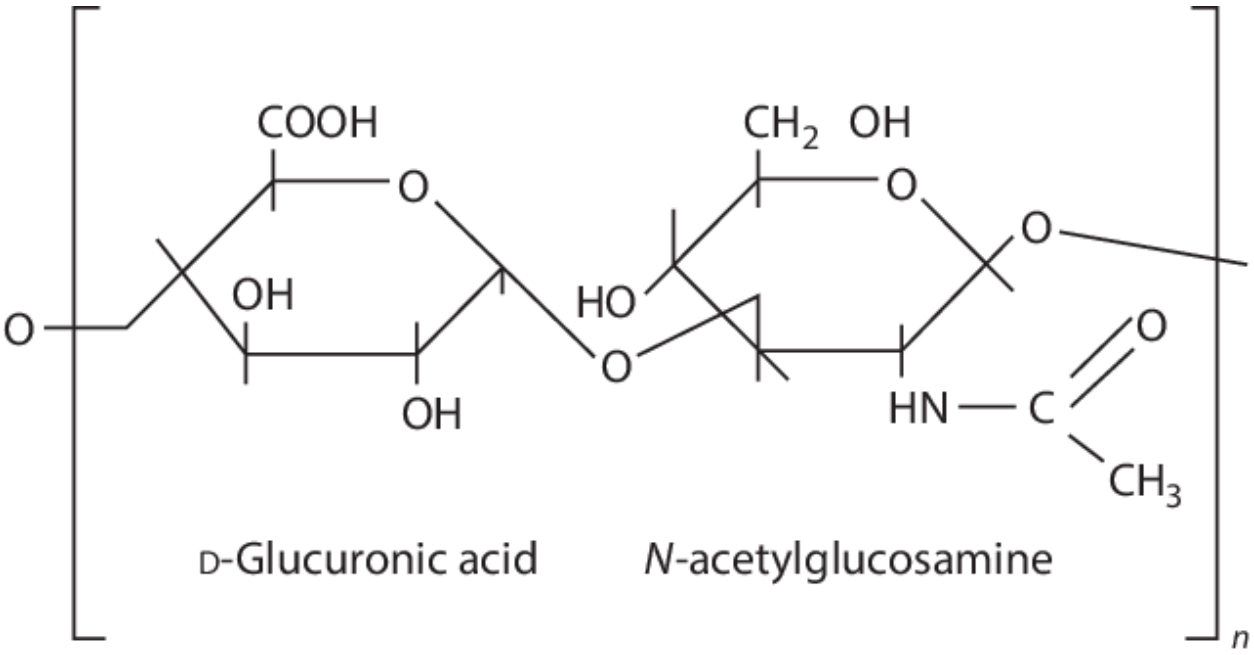


Figure (1-4): The chemical structure of hyaluronic acid. (**Liu Z. et al., 2008**)

1.7.1 Properties of Hyaluronic Acid (HA)

The biocompatibility, non-immunogenicity with viscoelastic nature of Hyaluronic acid make it unique to be used in several clinical applications, such as a surgical aid to facilitate scar-free healing and regeneration of incision wounds, ability to reduce the penetration of viruses and bacteria into the tissue, also has been associated with several cellular processes, including regulation of inflammatory reaction and the angiogenesis. (**Liu Z. et al., 2008**).

HA has an effect to maintain healthy periodontal and peri-implant tissues,

also a beneficial effect in bone regeneration (osteo-inductive effects). (**Galli F., et al., 2008**).

Fibroblasts that are embedded in the deeper tissues have been associated with the biosynthesis of the HA-rich matrix. HA is involved in tissue repairing mechanisms. Also contributes to tissue hydrodynamics, cell migration, and proliferation. Hyaluronic acid has a major role in inflammation, tissue regeneration, and angiogenesis, these are phases of skin wound repair. thus promotes wound healing. (**Casale M., et al., 2016**).

1.7.2 Cell Surface Receptors for Hyaluronic Acid

There are three groups of cell surface receptors that have been recognized for HA; Cluster of differentiation-44 (CD44), the receptor for HA-mediated motility (RHAMM), and intercellular adhesion molecule-1 (ICAM-1). (**Litwiniuk M., et al., 2016**).

CD44 is the main cell surface receptor for HA and is widely distributed throughout the body, CD44 mediates cell interaction with HA and functions as an important part in physiologic events such as cell migration, proliferation, and activation. Two major roles of CD44 in the tissues were suggested; regulation of keratinocyte proliferation, and maintenance of local HA homeostasis. (**Ievdokimova N. 2008**).

RHAMM is a protein that altered migratory cell behavior as it binds to HA. It can cooperate with CD44 to promote angiogenesis by promoting the migration of adjacent endothelial cells. (**Litwiniuk M., et al., 2016**).

ICAM-1 is a glycoprotein receptor for Hyaluronic acid and is expressed on endothelial cells and cells of the immune system. this protein is responsible for the clearance of HA from lymph and plasma, which accounts for most of HA turnover (degradation and synthesis). (**Litwiniuk M., et al., 2016**).

ICAM-1. serves as a cell adhesion molecule, and the binding of Hyaluronic acid to this receptor can contribute to ICAM-1-mediated inflammatory modulation. (**Ievdokimova N. 2008**).

1.7.3 The Role of Hyaluronic Acid in Scar-Less Wound Healing

1.7.3.a Extra-cellular Matrix (ECM) Regeneration

Deposition of collagen by fibroblasts is considered one of the features in constructing a supporting matrix at the sites of scar tissue formation (collagen deposition is enhanced and ordered following the application of hyaluronic acid). raised levels of Hyaluronic acid at the sites of injury seem to decrease the contraction of fibroblasts. (**Price RD. et al., 2007**).

1.7.4 Epithelial Regeneration

Increased keratinocyte proliferation and motility following the application of Hyaluronic acid. There is evidence of synergistic effect with the actions of endothelial growth factor. (cell migration is enhanced after Hyaluronic acid has been added). (**Price RD. et al., 2007**).

CHAPTER TWO

Discussion

(**Trombelli L. et al., 2018**), found that early mucosal healing was evaluated during the first 15 days, and described bacteriostatic and anti-inflammatory properties of hyaluronic acid, also his role in facilitating cell migration and differentiation and angiogenesis during tissue repair, this finding was consistent with (**Casale M., 2016, and Yıldırım S., et al., 2018**) who reported beneficial effects of topically applied hyaluronic acid in gel form in oral surgery.

Galli F., et al., 2008, concluded that single-dose application of hyaluronic acid over surgical incision wounds intraorally does not improve wound healing. In contrast, (**Yıldırım S., et al., 2018**), showed that topical application is a beneficial and supportive method in accelerating epithelialization of second-intention wound incisions.

(**Casale M., et al., 2016**), in their systematic review concluded a multifunctional role of hyaluronic acid in scar-free wound healing, also its application in the postoperative healing period, and its valuable treatment for treating oral ulcers, they emphasized that topical treatment was more effective in delivering high concentrations of the medicament to the area of interest, rather than systemic administration.

(**Parker NP., et al., 2009**), demonstrated that the use of HA in gel form gives more organized connective tissue, improved epithelial closure, and decreased inflammation as compared to controls.

It is widely reported in the article of (**Ciccone V., et al., 2019**), that Hyaluronic acid, due to its structural role, keeps tissues hydrated and maintains the osmotic balance, also regulates cellular processes as adhesion, migration, and proliferation thus improves tissue hydration and resistance to mechanical stress.

(**Litwiniuk M., et al., 2016**), demonstrated that Hyaluronic acid presented through all steps of the process of wound healing therapy as a factor that modulates tissue regeneration. An effective wound healing process is regarded as one of the greatest challenges in modern clinical medicine. Hyaluronic acid regulates tissue repair at multiple levels and should be considered as a safe and effective option to be used in secondary intention wound incisions.

CHAPTER THREE

CONCLUSIONS

Research into HA's role in wound healing is an evolving science. Much of the early research reviewed appeared to focus on HA's role in scar formation and its presence in skin. As scientific research of each phase and process of wound healing has progressed, understanding of HA's roles has deepened, implicating it in every major wound healing event.

HA's functions during wound healing change with its size. Large, heavy and long HA chains appear to have structural functions such as porous networks during inflammation and as a space filler in granulation tissue. This contrasts with the small, light and short HA fragments that have stimulatory and attracting properties such a fibroblast migration and collagen production .

The influence of HA on clinical practice can be viewed in differing ways. From a purely educational perspective, HA gives the clinician insight into the physiological depth of wound healing because of HA presence in many wound healing processes. When this cellular understanding is applied to HA research, the clinical context of wound treatment is promoted from a series of biological events to a real-time science.

Care must be taken when applying the reviewed HA research clinically, as some of the research reviewed does not replicate clinical conditions. Wound research, however, is challenging to perform in real-life conditions. Apart from the ethical and financial considerations, due to the complex nature of wound healing, consistency in human wound healing research can be difficult to attain . These limitations aside, many clinical applications such a scarless healing and HA-based dressing can be drawn from the reviewed research, with promising future developments.

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