Heliyon 6 (2020) e03722

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Biological molecules in dental applications: hyaluronic acid as a companion biomaterial for diverse dental applications

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ARTICLE INFO

Keywords:
Materials science
Dentistry
Natural product chemistry
Biotechnology
Biochemistry
Hyaluronan
Hyaluronic acid
Dental treatments
Advances in dentistry
Regenerative dentistry
Glycoproteins
Carbohydrates
Extracellular matrix
Polymers

ABSTRACT

Objectives: The application of hyaluronic acid (HA) in dental treatments is relatively new, and modified-HA products can be vastly different from each other. This study aims to provide a basis for bridging specific characteristics of HA with its potential applications in dental treatments, evaluating and comparing different types of HA products and for future research on HA applications in dentistry.
Data sources: Information from the existing literature on HA applications has been cited.
Study selection: Furthermore, this study is specifically oriented to provide oral health care providers with a scientific basis for HA use along with the clinical aspects of HA.
Conclusions: Outcomes from existing and future studies cannot be generalised for HA use in dental applications. Therefore, we have proposed a scheme to bridge HA specific characteristics to its applications in dental treatments and compare different HA products used for the same clinical application to identify the most suitable one.
Clinical significance: Highlighting the use of HA in dental treatments and providing a basis for developing new methods, protocols, and products specifically oriented for dentistry.

1. Introduction

Hyaluronic Acid (HA) is a special type of glycosaminoglycan (polysaccharide, carbohydrate) and an interesting biomolecule. It has been used in many medical applications, including cosmetics, aesthetic treatments, and treatment of interstitial cystitis, urinary incontinence, vesicoureteral reflux, and osteoarthritis. Studying the essential molecules of living organisms (including HA) includes knowledge of their sources in nature and methods of synthesis within an organism or artificial synthesis, the study of their chemical and physical structures, biochemical reactions, cellular pathways and interactions, and their association with the organism's developmental stages, nutrition, anatomy, and physiology. Furthermore, it includes the study of their influence on genetics, health, diseases states, gender, and age, and how they are affected by environmental factors. Finally, the same biological molecule can be compared between different organisms (species). It is worth mentioning that biophysics provides the knowledge of the biomechanics of molecules, tissues, and organs, and how these systems work within an organism.

In this study, we have briefly mentioned the characteristics of HA, and focused on the possible applications of HA as a biomolecule along with proposing a scheme to bridge its specific characteristics to its applications in dental treatments and to compare different HA products to identify the most suitable one for particular procedures.

2. Discussion

2.1. Structure and functions of biomolecules

An important characteristic of biomolecules is that they can exist in multiple conformational forms, mainly due to the different types of bonds between their individual elements. For instance, glycogen, starch, and cellulose are all made of glucose units linked by 1–4 glycosidic bonds. In glycogen and starch, the link is at the alpha position, but in cellulose, it is at the beta position. The bond configuration affects the geometry of the molecule resulting in a banded helix for glycogen and starch, so that it occupies minimal volume in the cell as they are intended for energy storage, whereas cellulose forms an extended shape as it is intended to

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https://doi.org/10.1016/j.heliyon.2020.e03722
Received 24 January 2020; Received in revised form 2 March 2020; Accepted 30 March 2020

provide mechanical integrity to the cell wall in plants [1]. Thus, we can say that 'a specific structure is proof of a specific function, whereas a specific function requires a specific structure' [2].The extra cellular matrix (ECM) is composed of many biomolecules and proteins, all composing a sophisticated network. ECM composition and organisation are tissue-specific and correspond to specific physiological and biochemical functional properties. Naturally, this specificity tends to be expressed as the specific rate of synthesis and degradation in different tissue types and species. For instance, in humans, the HA half-life in the joints, epidermis, and blood is 1–30 weeks, 1–2 days and 2–5 min, respectively [2, 3]. The difference in HA half-life in ECM of different tissues is due to its different conformational forms owing to association with different biological molecules. The ECM stands for the framework where cells can attach themselves and perform their physiological functions [4].

2.2. Importance of HA in human body

HA $(C_{14}H_{21}NO_{11})_n$ is a homogenous unbranched glycosaminoglycan composed of repeated disaccharides. In the human body, HA biopolymer (native HA) constitutes a major component of the extracellular matrix (ECM), and can be found in many different tissues [2, 5]. Native HA, as a biomolecule, is present in oral tissues, such as the gingiva and the periodontal ligaments (synthesised by fibroblasts and keratinocytes), and in low quantities in cementum and the alveolar bone (synthesised by cementoblasts and osteoblasts). Furthermore, HA is present in the saliva with a concentration in the range of 148–1270 ng per milligram of protein in the unstimulated whole saliva [2, 6]. This variation in HA levels is mainly due to variations in the individual diet, oral hygiene, genetics, oral anatomy, health and disease state, and others.

Different concentrations and molecular weights of HA (tissue dependent) triggers different cell responses. In general, high-molecular-weight HA (>5 Million Da) has an anti-angiogenic and immunosuppressive effects. Medium-size HA (2×10^4–1 Million Da) is associated with certain biological processes such as embryogenesis, wound healing and regeneration. Small-size HA (6×10^3 Da–2 x 10^4 Da) is associated with different cellular processes (e.g. pro-inflammatory, angiogenesis and gene expression). Small strands of HA can act as inducers of the heat shock proteins and an anti-apoptotic agent [7].

HA is naturally synthesised by the proteins (HA synthases), which are of several types in human: HAS1, HAS2, and HAS3 [6,8]. In the human body, the hyaluronidase enzymes, which are also of several types, are responsible for enzymatic degradation of HA. It is estimated that 85% of the HA is turned over in the lymph nodes, and the rest is removed by the liver and kidneys [9, 10]. Complete HA degradation yields CO_2, NH_3, acetate, and lactate, which are further metabolised by hepatocytes to CO_2, H_2O, and urea. Native HA molecule along with its receptors, HA synthases, and HA hyaluronidases, are all tissue-specific and dependent on the developmental phase, gender, age, health/disease state, and environmental factors [9, 11, 12, 13].

2.3. Natural sources of HA

HA can be obtained either by extraction from animal tissues (usually rooster combs) or from certain bacterial strains which naturally produce HA (mainly *Streptococcus zooepidemicus*) or that have been genetically modified to (e.g. *Bacillus, Agrobacterium*, *Escherichia coli*, and *Lactococcus*) produce HA [14]. The process of HA extraction includes the associated risk of having sources of contamination, such as viruses and animal proteins (HA extracted from animal sources), and toxins along with bacterial proteins (HA extracted from bacteria). Such sources of contamination may trigger an immune response. As per recent reports, marine organisms are a possible resource for HA [7, 15, 16].

2.4. Modification of native HA

Although, due to extraction methods used, the conformation of the extracted HA may be different from that of the native HA *in vivo,* it is the closest form to native HA and can be used for certain medical applications, where such forms of HA are often degraded quickly by hyaluronidases. For some medical applications, the extracted HA must be chemically modified to serve certain cellular or physiochemical properties. A good example is the chemical modification of HA used in intra-articular injections, where the residence time (product-dependent) extends from weeks up to a year after administration of HA into the articular joint.

Generally, the purpose of HA modification is as follows:

- To enhance its resistance to degradation, and thereby enhancing its residence time and the duration of its effects [17].
- To adjust some of its properties, such as viscosity, elasticity and hydrophilicity, to meet certain physiochemical and mechanical properties [18].
- To have the HA in the final form of a gel or hard textured scaffold with specific pore and particle sizes for specific cellular functions (such as cell adherence or migration) [19].
- To create HA-drug conjugates and micelles for sustained or targeted drug release [20, 21].
- To link HA to natural or synthetic compounds (e.g. proteins, natural polymers, liposomes, synthetic polymers, drugs, and so on.) to achieve certain physiochemical or therapeutic properties [22].

There is a wide array of technical and chemical methods used to modify HA, each resulting in specific geometry having certain conformational form and physiochemical characteristics. Those physiochemical characteristics are affected by many factors, including the source of HA, manufacturing technique, HA molecular weight distribution, modification method, chemical agents used during the manufacturing process, purity of HA, and mixing the HA with other materials (if applied). This cumulatively affects the method of administration, degradation, residence time, and possibly the route of elimination of the product. Accordingly, a biocompatibility profile (including purity, toxicity, impurities, etc.) should be established for a modified HA. A famous method is the cross-linking process, in which the HA chains are joined through chemical covalent bonds. Cross-linking processes lead to the formation of 3-dimensional (3D) HA networks having modified physiochemical properties, particularly resistance to degradation, which results in a prolonged life span in the treated tissue [23].

Review of the available literature for HA use in dental applications revealed controversial and contradictory outcomes and variable data due to the large variety of molecular weights, methods of modification, and HA concentrations reported by previous studies [24]. Therefore, the outcomes from existing literature cannot be generalised for HA use in dental applications. In fact, a recently published systematic review [25] concluded that further well-designed randomised clinical trials will be needed to evaluate HA use in various clinical scenarios. As the exact biological functions of HA are still not well understood, there is a necessity to develop new methods to identify its structure in living tissues, interactions with other molecules and receptors and to better understand its association with cellular functions [2].

From clinical aspect, future studies should seek to compare different HA formulations used for the same clinical application to identify the most suitable one. To our knowledge, only two published studies have tested different HA preparations for dental applications. The first study (Vandana and Singh, 2019) [26] tested the effect of different HA concentrations on interdental papillary deficiency treatment and the second study (Asparuhova et al., 2018) [27] tested two different HA preparations on primary human oral fibroblasts.

Researchers should make all efforts to study, test, and report HA characteristics and modifications to enable other researchers compare

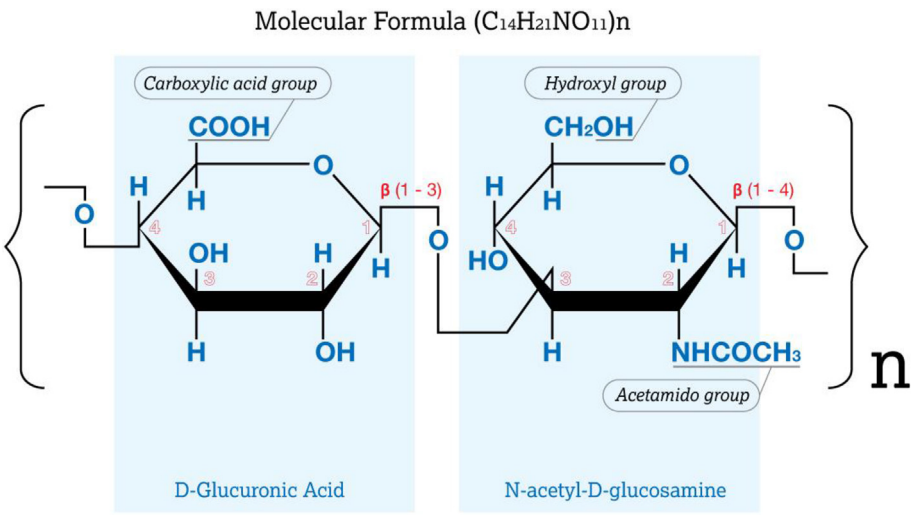

Figure 1. Chemical structure of HA showing the chemical groups that can be modified.

different types of HA. In addition to these characteristics, it is important to study and report the microscopical appearance (transmission electron microscopy for its supramolecular organisation and scanning electron microscopy for its surface topography, fibrillar organization, and porosity) and its UV absorption spectra [2].

From the chemical standpoint, there are three chemical groups on the HA chain that can be modified: the carboxylic acid group (COOH), hydroxyl group (OH), and the N-acetyl group (CH_3CO) which is located on the acetamido group (C_2H_4NO) [23]. Note that the N-acetyl group contains a methyl (CH_3) and carbonyl (C=O) group. Figure 1 shows a diagram of HA and its chemical groups that can be modified.

Depending on method(s) of modification, the applications of HA has a wide spectrum of possibilities, such as in wrinkle treatment, ophthalmic surgery, drug delivery, wound healing, cartilage, and bone regeneration, etc. [7]. We should draw attention that the HA elasticity and viscosity constitute the practical aspect where their behaviour provides expectation for their performance under physiological conditions, and thus provide the basis to select an appropriate HA product for the clinical treatment. Furthermore, the rheological properties of biological fluids along with the biomechanical properties at the cellular-, tissue- and organ-levels are important to draw an overall understanding of the mechanism by which the entire body system works and can give excellent insights for possible treatments and for related materials. Regarding oral tissues for instance, the elasticity of the dental enamel is in the range of 1030–1646 MPa, whereas it is 1376–1932 MPa for the dental dentin [28]. At the cellular level, human mesenchymal stem cells can differentiate into neurogenic phenotypes if cultured on a hydrogel with viscoelasticity similar to that of the brain (0.1–1.0 kPa), but they differentiate into myogenic phenotypes on hydrogels with viscoelasticity similar to that of the muscles (8–17 kPa). The stem cells of periodontal ligament, dental pulp, and apical papilla can differentiate into osteoblasts, chondrocytes, or neurocytes depending on the nature of trigger and medium in vitro. Thus, the different rheological properties of HA-based gels can trigger different cellular responses [2, 29, 30].

2.5. Considerations for use of biomaterials specific to dentistry

When investigating biomaterials and their medical applications, they are intended to replace, enhance, adjust, mimic or modify a biological function using a synthetic (metal, polymer, etc.) or biological material, either as a standalone material or mixed with other biological, natural or synthetic one. Broadly speaking, biological materials (including HA) used in dental applications are mainly intended to regenerate soft tissues, work as a physical barrier between soft and hard tissues (bone), assist in wound healing and regenerate hard tissues.

Dental procedures related to the regeneration (for soft and hard tissue) and wound healing are broadly divided into two groups: 1) surgical procedures including treatment for sinus lifting, surgical treatment for periodontitis, bone grafting and regeneration, surgical treatment for gingival recession, and socket preservation. 2) non-surgical procedures including treatment for papillae regeneration, non-surgical treatment for periodontitis, mouth ulcers, and gingivitis [31].

For both, surgical and non-surgical procedures, and in relation to regeneration and wound healing, four major factors are needed for optimum outcomes: 1) viable cells as building blocks, 2) the trigger or chemical signal to start and stop the cellular processes, 3) angiogenesis to supply needed nutrients and eliminate cellular waste, and 4) scaffold as a cast for cells to grow in 3D [32]. With regard to these factors, HA (modification dependent) can function as a gel scaffold, trigger, or even as a reservoir for releasing chemical signals (such as hormones or growth factors). HA as a standalone material does not have enough mechanical integrity; therefore, the three possible functions (as gel scaffold, trigger, and reservoir) represent its main applications, as a companion biomaterial to dental procedures, particularly those related to regeneration and wound healing.

Scaffolds (rigid forms and gel forms) should have certain characteristics to enable the cells to adhere to them and grow, and they should be biocompatible and biodegradable. For hydrogel scaffolds (including HA gel scaffolds), their mode of action depends on their physical and biological characteristics [33, 34].

Growth factors are biological molecules which trigger the cells and enzymes during biological processes, but they cannot form a 3D material as they are not structural in their nature. Nevertheless, they can reinforce the basic 3D scaffold. An appropriately designed HA scaffold can work as a reservoir for growth factors, thus containing the cellular triggers and simultaneously releasing the factors over a certain period, depending on its design and on many factors related to the final form and physiochemical properties of the HA molecule as previously mentioned [35]. Generally, a modified cross-linked HA is often first anti-inflammatory in function upon its introduction into a tissue. Upon its degradation, depending on the type and degree of its modification, it may trigger different cellular functions.

From practical and clinical dental treatment viewpoints, there are some other factors to consider regarding the use of biological materials (including HA). Most dental procedures related to regeneration are expected to give basic outcomes (in relation to regeneration time) within 3–6 months of the treatment, and are procedure dependent; therefore, similar or earlier result time frames are expected with the use of biological materials. However, this may not be the case; for instance, if the residence time of a biological material is very short, it may not generate

Level 1: Natural material used	Level 2: Native molecule characteristics	Level 3: Modified molecule - general check points	Level 4: Modified molecule – specific check points	Level 5: Modified molecule – detailed physicochemical properties, cellular effect, and clinical effect.	Level 6: Modified molecule – research and clinical studies.
Hyaluronan	Native molecule functions.	Product biocompatibility profile including its purity, content of proteins, toxins, impurities, etc.	Product mode of application.	Rheological, biomechanical, and physiochemical properties including solubility, osmolality, particle size, swelling capacity, viscosity, elasticity, compressive strength, pores size, and diffusion.	If no enough information: conduct research to fully examine the product including (physical and chemical characteristics, in vitro, animal, and clinical studies).
	Native Molecule physical and chemical structure and its natural functions.	Is there any in vitro studies and animal studies ?	General characteristics of the product final form related to its application and use.	Final product geometrical (3D) form and its surface topography – if it has one.	Find out exact biological properties and cellular functions including cellular receptors for the final product.
	Native molecule biochemistry and metabolic pathways.	Is there any initial human trials ?	Contents in the product final form (if any) other than HA.	The product effect on different types of cells in terms of cells adhesion, motility, growth, differentiation, proliferation, and migration (in vitro studies).	Find out the product interactions with other cellular molecules, other factors, other substances, etc.
	Native molecule cellular pathways and cellular receptors.	Is the product licensed for sale or still not ?	HA concentration .	If the final HA product is cross linked: what is the cross linking method, degree of cross linking, and type of cross linker ?	Conclude the overall clinical value of the product and its possible uses.
	Native molecule and its relation to organism physiology and anatomy.	Product general indications and contraindications.	HA average molecular weight.	Suitability of the product and its use in clinical procedures.	Based on information acquired, check if the product indications, uses, mode of application, and efficacy, can be extended or adjusted. Compare different products which are used for same clinical application.
	Native molecule and its relation to (genetics, age, gender, environment, disease).	Targeted tissue, age category, gender, etc. for treatment.	What is the purpose of modification to native molecule?	Is the application of the product invasive or not ?	Important note: Take note for all possible information before use of the material in order to know exactly how to use it.
	HA product source (animal, bacterial, etc.), and production method used.	Product mode of action.	What is the technique of processing or modification including the targeted functional groups?	Suitability of the product for some factors specific to dentistry such as contact with saliva, blood, swallowing, bacteria, etc.	
		Product final form (solution, gel, gel scaffold, hard scaffold).	Hydrophilicity/hydrophobicity profile for the final product.	Do the product meet the clinical outcome time frame in comparison with the standard treatment and its outcome ?	
		Product storage conditions.	Exact clinical and cellular effect (if known).	Overall advantages and disadvantages and assessment against the 4 factors (viable cells, trigger, angiogenesis, scaffold) for its possible clinical uses.	
			Residence time (if known).		
			Turnover rate, degradation, and elimination (if known).		

Figure 2. Scheme of considerations for use of a HA product.

the desired effect. Additionally, it is very common for blood to spread over the treated area what makes its complete isolation impossible. Accordingly, this factor (possibility of mixing with blood) must be considered when designing biological materials for oral applications. If the HA is in the form of a gel scaffold, mixing with blood is considered beneficial as it will possess an intrinsic reservoir of the biological factors contained in the blood. Also, the possible effects between saliva and the biological material should be considered in case of direct contact between them. Finally, one of the most important factors is the continuous existence of bacterial communities, which should be considered carefully upon using biomaterials. Generally, HA have a bacteriostatic effect which manifests by neutralising bacterial hyaluronate lyase enzymes and is applicable with dental implants. Designing HA with a bactericidal agent can be very beneficial for certain clinical cases where high local concentration of the bacterial agent over a certain period is required.

Considering HA as a biological material depends on its final form and characteristics. It can be used as a standalone material to trigger certain cellular functions, a 3D gel scaffold for cells growth and differentiation, gel scaffold working as a physical barrier between soft and hard tissue, gel scaffold containing growth factors or other natural factors (bone morphogenic factors, fibroblast growth factors, platelet-derived growth factors) released over certain time and/or concentrations, carrier for drugs ensuring their sustained release, and co-material with other biological (fibrin, collagen, chondroitin sulphate, hydroxy apatite), natural (cellulose, chitin, starch, alginate, silk), or synthetic materials for enhanced function of either entity. HA applications in dental procedures vary widely, and one should always keep in mind the four essential factors (cell viability, type of cellular trigger, angiogenesis, physicochemical characteristics of the scaffold) required for regeneration or wound healing as evaluation tools when exploring the possible applications or expected outcome results of a natural biomaterial [30, 36].

Some examples on HA uses in dentistry include:

- Injecting HA for papilla regeneration [37].
- Covering the dental implant with HA to enhance its osseointegration.
- Mixing the HA (recommended mixing ratio 1:1) with synthetic bone grafting material for sinus lifting, socket preservation, and periodontal regeneration procedures for enhanced bone growth, even distribution, and increased density of the newly formed bone block [38].
- Covering the surgical area (from inside and outside) by HA to enhance and to accelerate the tissue healing process (including surgical gingival recession treatment) [39].
- Using HA after scaling and root planning as an adjacent therapy for periodontitis.
- Topical application of HA for treatment of oral ulcers.
- Using HA as an adjacent to gingivitis and peri-implantitis treatments.
- Using HA as an adjacent to non-surgical gingival recession treatment.
- Mixing HA with platelet-rich fibrin, plasma, and growth factors to enhance overall outcomes [40].
- Using HA as a nano-sized drug carrier [41].
- Using HA as a matrix to encapsulate stem cells and signalling molecules for reconstruction of temporomandibular joint, salivary glands, dental pulp, dental bone, enamel, root-canal, and mucosa [42, 43, 44].

Practically, physicians may need to compare between available HA products to identify differences in terms of their clinical use. Thus, it is logical to provide a model scheme (Figure 2) summarising the relevant considerations for evaluation of an HA product, in anticipation of its possible uses and expected outcomes. This scheme can be used or modified for use with any biological or natural material with generally similar characteristics.

It is worth mentioning that the scheme (Figure 2) has been designed for use by oral care providers as a checklist of different levels depending on available information. Upon knowledge of exact characteristics of the material in use and considering mentioned parameters, it can be bridged with its possible application in dentistry. At the same time, this scheme (Figure 2) can be reversely used in designing a product which matches the desired features of the planned therapy.

3. Conclusion

The biological properties of HA depend on many parameters, and thus it is important for oral care providers to be able to compare between different products. This study provides the scientific background for HA use and a model scheme as a basis to bridge specific characteristics of HA with its potential applications in dental treatments. Comparison of the proposed parameters constitutes a basis for development of new methods, protocols, and products specifically oriented for dentistry.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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