Applications of Hyaluronic Acid (HA) in Dental Implant Treatment: A Systematic Review

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ABSTRACT

Introduction: Hyaluronic acid (HA) has a long history and is widely used in cosmetics, medicine, and dermatology. This molecule is still considered relatively new in the field of dentistry. This study aimed to assess the application of HA in dental implant treatment. Method: Search in the multiple indexed databases such as Pubmed, COCHRANE, and Scopus was conducted up until August 2022 using the keywords “hyaluronic acid”, “hyaluronan,” and “dental implant.” Results: The literature search identified 816 articles, and 17 were selected in this study. Three domains of use of HA in dental implant treatment were identified: surface modification of implant surface, treatment after insertion of a dental implant, and bone graft/membrane material. There are eight randomized control trials and nine non-randomized control trials included in this study. Only six studies showed statistically significant results with HA groups. Conclusion: Overall, there are positive findings on the application of HA in dental implant treatment, showing it can be used in dental implantology, with multiple categories of uses. Keywords: Hyaluronic acid, Hyaluronan, Dental implant, Dentistry

INTRODUCTION

The dental implant is a predictable method used to replace a missing tooth or a compromised tooth. A tooth is usually extracted due to caries, periodontal diseases, or trauma (1, 2). There was a long history of the implant to restore the missing tooth, from the ancient era until the modern age (3). The modern dental implant was based on Bremenkar’s work on osseointegration in the 1980s. This important work was pivotal to modern dental implants with huge success (4). The published articles reported a simple success rate of 95% (5). This treatment modality is now highly predictable with a long-term success rate, with a relatively small number of pus discharge cases or peri-implantitis (4). There were several factors listed by Griggs et al. that influenced the success of dental implant treatment (5). This includes publication bias, the location where the treatment is done, and technical parameters during implant placement like torque, the implant design, bone augmentation procedure, or surface treatment of the implant material.

Hyaluronic acid (HA) or hyaluronan (C14H21NO11)n is a particular type of nonsulfated glycosaminoglycan (GAG) (6, 7), homogenous unbranched GAG with repeated disaccharide (6). It is present naturally in animals and humans and has the fantastic ability to hold up to 1000 times the weight of water (7). Native HA is present in the human body as a significant component in the extracellular matrix (ECM) and can be found in many tissues (6, 8). HA functions in moisturizing the tissues and keeping the viscoelastic form of ECM (9). In pharmacology, HA is a versatile substance with a wide range of activities such as anti-inflammatory (10), bone regeneration (9), wound healing (11), oral ulcer (12), tissue regenerative, immune modulation, anti-cancer, anti-diabetic, anti-aging, cosmetics, and skin repair (7). Due to its astounding water-retaining effect, HA is widely used in dermatology and cosmetics, such as in many moisturizing, skin-protecting, and anti-aging products (7).

HA can be found in all living organisms, as it is one of the components of the extracellular matrix (13). In the oral tissues, HA can be found abundant in the gingiva and periodontal ligament, with low concentration in cementum and alveolar bone, as well as in saliva. There are many actions for HA, depending on its molecular weight. Low molecular weight HA is associated with pro-inflammatory and angiogenesis response by signaling tissue damage and recruiting inflammatory cells (6, 12). Medium molecular weight HA has been seen in embryogenesis, healing of the wound, and
tissue regeneration (6). Meanwhile, high molecular weight HA has anti-angiogenic and suppresses the immune response and consequently inhibits excessive inflammatory actions (6, 12).

HA is commonly extracted from animal tissue, marine organism, or bacterial production, but it may be exposed to contaminations and toxins, (14) and it is also different from the native HA in human tissues. Bioengineered synthesis of HA from an enzymatic process is a much simpler procedure and reduces the risk of contamination. For example, HA can be biosynthesized from Streptococcus zoopneumoniae bacteria (8). However, some modifications need to be done for the extracted HA to make it compatible with human tissues (6). There are many ways of modifying the extracted HA to make it compatible with human tissues and reduce the degradation by hyaluronidase and other medical applications (6, 15). The multiple methods resulted in a variety of HA molecular weight, extraction, and modification methods in HA research. For that, Al-Khateeb and Olszewska-Czyz proposed a six-level of research model for HA application in dentistry since the processes from the discovery of native HA to the clinical application are too long (6).

In dentistry, the research for HA application is still relatively new (6). The early publications in the 1990s and early 2000s focused on peri-implant sulcus fluid glycosaminoglycan (GAG) analysis for tissue response and healing after implant placement (16, 17).

HA was reported to have a bactericidal effect, and linking HA with other antibiotic agents may be beneficial in the dental implant (6). The viscoelastic property of HA reduces bacterial and even viral penetration into the tissues (12). Among other applications of HA concerning dental implant treatment include layering of the implant surface to increase osseointegration, mixing HA in bone graft material, covering the surgical site with HA to increase healing, peri-implantitis treatment (6), and bone regeneration (9). Topical applications of various forms of HA have proven beneficial for post-operative dental treatment, inflammatory gingival, and periodontal diseases, which could be essential for a successful dental implant case (12).

This article aims to report the research accomplished regarding HA and dental implant treatment. Any available or possible applications of HA for dental implant treatment were to be explored. It is hoped that future researchers can anticipate the development and usage of HA in the implantology discipline.

METHODS

Study Design: The systematic literature search made according to PRISMA Guideline (18) with these criteria was conducted in August 2022, where peer-reviewed articles were published in the English language, research articles involving human studies. Review, technical notes, and letters to editors were excluded. Further methodological guidance for conducting a systematic review article by Mohamed Shaffril et al. was also followed (19).

Information Source and Search Strategy: PubMed, Science Direct, and Cochrane database were searched for relevant studies using these keywords or medical subject headings: (“hyaluronic acid” and “dental implant”), (“hyaluronic acid” and “implantitis”), (“hyaluronic acid and mucositis”), (“hyaluronan” and “dental implant”) without any time limit for the publication. The research question is, can hyaluronic acid be used for dental implant treatment, and what are the applications? The PICO (Population, Intervention, Comparison, and Outcome) elements are described as follows: Population: studies that included hyaluronic acid for dental implant treatment; Intervention: addition or incorporation of hyaluronic acid; Comparison: standard reference; Outcome: clinical observation, clinical indices, radiographic and histomorphometric examination.

All articles that resulted in the search were screened according to title and abstract, and only relevant articles were screened with full articles. The article selection, data extraction, and risk of bias assessment were done independently by two authors, AB and NI. Should there be any disagreements, a discussion was done by the two authors to decide on the article selection, data extraction, and the risk of bias assessment. Double data checking was also conducted to ensure no duplication and the correct data entry.

Quality and Bias Assessment: All articles were screened and classified according to the research methodology and its application in dental implant treatment. All articles related to human subjects were divided into randomized control trials (RCT) or non-randomized control trials (non-RCT), then further checked for the level of evidence based on the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (20). Only articles with at least level 4 until level 1 evidence according to the Oxford guideline were selected. Risk of Bias Assessment were done using the COCHRANE Risk of Bias assessment tool (21).

Inclusion and exclusion criteria: Studies that only measured the HA in GAG post-dental implant surgery, not experimenting with HA, including samples from animal groups or not related to dental implants were also excluded. There were no exclusion criteria of outcome used for forming criteria in this article.

RESULTS

There were 17 articles, both with RCT and non-RCT
designed to include in this review, as shown in Figure 1. Then, we further group the articles into different categories, regarding modification of dental implant surface with HA, bone graft or membrane material incorporating HA, and treatment after dental implant procedure with HA. Table I summarizes the publications selected. All articles scored at least level 1 according to the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence. The risk of bias assessment is presented in Table II. Only three out of 17 studies scored low risk of bias for all components. The other studies recorded mixed unclear risk of bias and high risk of bias.

**DISCUSSION**

HA is a versatile molecule that has vast medical applications. There are already several commercially available HA-based products available in dentistry, such as Gengigel and Aftamed, which is used to treat oral ulcer (22, 23). However, the application of HA for other types of dental treatments is still relatively new.

<table>
<thead>
<tr>
<th>Table I: Applications of HA in dental implant</th>
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<tbody>
<tr>
<td>Author/Year</td>
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<tr>
<td>Implant surface treatment</td>
</tr>
<tr>
<td>Lupi et al., 2019 (22)</td>
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<tr>
<td>Treatment after implant insertion</td>
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<tr>
<td>de Araujo Nobre et al., 2007 (23)</td>
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<td>Lopez et al., 2017 (24)</td>
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<td>Lopez et al., 2017 (25)</td>
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<td>Genovesi et al., 2017 (26)</td>
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<td>Trombelli et al., 2018 (27)</td>
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<td>Kaya et al., 2019 (28)</td>
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**Table I: Applications of HA in dental implant (continued)**

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study type</th>
<th>Study method</th>
<th>Characteristic of intervention</th>
<th>Analysis done</th>
<th>Outcome/Key Findings</th>
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<tbody>
<tr>
<td>Soriano-Leirma et al., 2019 (29)</td>
<td>RCT</td>
<td>54 patients with 108 samples. Three groups of treated with 0.8% at the office and 0.2% HA at home, placebo, and control. Review after 45 days</td>
<td>application by syringe of 0.8% HMW-HA gel</td>
<td>165 RNA sequencing techniques</td>
<td>HA reduced the relative abundance of peri-implantitis-related microorganisms. The use of HA in advanced stages of peri-implantitis resulted in a decrease in microbial alpha diversity, suggesting a protective action of the peri-implant site against bacteria colonization.</td>
</tr>
<tr>
<td>Capodieferro et al., 2020 (30)</td>
<td>non RCT</td>
<td>80 cases of endosseous dental implants with gingival flap elevation; of these, 40 were inserted into the experimental subgroup, which was treated with Aminogam® (five applications per day) until the gingival healing another 500 cases for other surgical procedures. Review until healing is achieved.</td>
<td>Aminogam gel containing sodium hyaluronate and four synthetic amino acids (glycine, leucine, proline, lysine)</td>
<td>Histological</td>
<td>This research includes seven types of dental surgeries and dental implant placement is one of them. The overall time of healing is certainly reduced in cases receiving Aminogam® gel in dental implant placement, and other types of surgeries too.</td>
</tr>
<tr>
<td>Sánchez-Fernández et al., 2021 (31)</td>
<td>RCT</td>
<td>61 patients with 100 implants diagnosed with peri-implantitis received either 0.8% HA gel, excipient-based gel, or no gel. Review up to 90 days.</td>
<td>0.8% HMW-HA gel</td>
<td>Clinical periodontal variables and marginal bone loss, IL-1β and TNF-α levels in the crevicular fluid</td>
<td>Reduced bleeding on probing. Topical application of a HA gel in the peri-implant pocket and around implants with peri-implantitis may reduce inflammation and crevicular fluid IL-1β levels.</td>
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**Bone graft/sinus lift**

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study type</th>
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<th>Characteristic of intervention</th>
<th>Analysis done</th>
<th>Outcome/Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwartz et al., 2007 (32)</td>
<td>non RCT</td>
<td>32 sinus lifts, divided into four groups: I: DFDBA + Bio-Oss, II: DBX (DFDBA in HA carrier) + Bio-Oss, III: DBX alone, IV: DBX + β-TCP. Preop and 8 months postop CT, and bone biopsy checked with histomorphometric analysis. Review after 8 months.</td>
<td>DBX hyaluronic acid carrier is used in several DFDBA formulations for sinus graft material.</td>
<td>CT and histomorphometric</td>
<td>HA improves the handling property of bone graft material and can be used as a carrier for DFDBA without reducing the clinical effectiveness of DFDBA. The bone quality is good and dental implants can be inserted in the graft area.</td>
</tr>
<tr>
<td>Butz et al., 2013 (33)</td>
<td>RCT</td>
<td>24 edentulous patients undergo a sinus lift with PepGen P-15 Putty. The healing time of two, four, six, or nine months were chosen randomly, Ten patients, one side of sinus lift with HA, while another side with an ultrasonic resorbable pin, reviewed after 6 months.</td>
<td>PepGen P-15 Putty, a combination of bovine hydroxyapatite and synthetic peptide in a sodium hyaluronate carrier</td>
<td>MicroCT and Histomorphometric</td>
<td>The accelerated healing time of up to 2 months post-operative procedure, where the dental implant can be inserted after 2 months. The common healing time is around 9 months.</td>
</tr>
<tr>
<td>Emam et al., 2015 (34)</td>
<td>non RCT</td>
<td>Ten patients for sinus augmentation using PepGen P-15 Putty comprises anorganic bovine bone matrix (ABM) coupled with a synthetic cell-binding peptide, suspended in a sodium hyaluronate carrier. Bone core was harvested at eight and 16 weeks.</td>
<td>PepGen P-15 Putty comprises anorganic bovine bone matrix (ABM) coupled with a synthetic cell-binding peptide, suspended in a sodium hyaluronate carrier.</td>
<td>micro CT and Histomorphometric</td>
<td>Increased bone height, bone density, and bone volume. PepGen P-15 Putty is capable of inducing and accelerating new bone formation and can successfully support dental implants. Possible shorter duration loading of the dental implant.</td>
</tr>
<tr>
<td>Gocmen et al., 2016 (35)</td>
<td>non RCT</td>
<td>Ten patients, one side of sinus lift with HA, while another side with an ultrasonic resorbable pin, reviewed after 6 months.</td>
<td>Hyaloss Matrix applied as space maintenance in the sinus.</td>
<td>CBCT: alveolar bone height and reduction in sinus volume</td>
<td>Sufficient bone height for both techniques, but better results in the resorbable pin group. The dental implant was successfully placed after 6 months.</td>
</tr>
<tr>
<td>Knabe et al., 2017 (36)</td>
<td>non RCT</td>
<td>Ten patients, one side of sinus lift with HA, while another side with an ultrasonic resorbable pin, reviewed after 6 months.</td>
<td>pure TCP granules embedded in a fermented sodium HyAco hydrogel matrix.</td>
<td>CBCT, Histomorphometry, and Immunohistochemistry</td>
<td>TCP-P showed greater expression of Col I and BSP and less volume reduction, and these may be related to the difference in grain size of the TCP granules and/or the addition of the HyAco. More superior handling, greater bone formation.</td>
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<tr>
<td>Dogan et al., 2017 (37)</td>
<td>RCT</td>
<td>13 patients requiring both sides of sinus augmentation, one side with HA and collagogen bone graft, the other with only collagenated bone graft. Review after 4 months.</td>
<td>hyaluronic matrix (HyAloMatrix) in addition to CHBG (1 g). Hyaloss is solid in the form of fibers that form a gel when hydrated, releasing pure hyaluronic acid.</td>
<td>MicroCT and histomorphometric</td>
<td>Increased bone formation in HA group with statistical significance through the use of hyaluronic acid-based matrix with CHBG for sinus augmentation, and the implant can be placed after 4 months.</td>
</tr>
<tr>
<td>Velasco-Ortega et al., 2021 (38)</td>
<td>RCT</td>
<td>24 patients, receiving either anorganic bovine bone mineral as control, tricalcium phosphate or without hyaluronic acid (HA), review after 9 months.</td>
<td>TCP plus crosslinked HA (Hyalident BG)</td>
<td>histomorphometric analysis, mean bone gain, intraoperative and post-operative complications, implant insertion torque, implant failure, and patient-reported outcome measures</td>
<td>The addition of HA did not influence the outcomes, with non-significant findings. An implant placed after 9 months.</td>
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</tbody>
</table>
HA hydrogel has vast potential in biomedicine. It plays an integral part in the process of tissue healing (13). The potential applications include cell delivery, drug delivery, and molecule delivery. Further applications through micropatterning, stem cell microencapsulation, and regenerative tissue engineering might be beneficial and can be further investigated (22).

In this review, the applications of HA in dental implantology can be divided into dental implant surface treatment, treatment after dental implant insertion and bone graft or sinus lift procedure.

**Dental implant surface treatment**

The paramount achievement in HA research for a dental implant is by having an RCT study of a dental implant unit with its surface treated with HA. Lupi et al. conducted a large number of samples with implants treated with HA and normal control implants with 36 months follow-up (24). The outcome showed that there is no significant difference between HA group and control normal titanium implant from clinical and radiographic examination. The authors have coated the titanium implant with HA from Nobel Bio Ricerche (Nobil Bio Ricerche srl, Portacomaro, Italy) via a covalent link that could stay longer on the implant surface and resist hyaluronidase action. HA-treated dental implant surface does not have any effects on the osseointegration of the dental implant and the bony tissue. The treated implant can be used in complex cases that require HA signaling and regenerative properties towards more pronounced peri-implant tissue healing.

Regarding the surface treatment of dental implants, the HA molecules were the layer that has contact with bone (24). HA was considered a carrier of osteoinductive and osteoconductive agents to help the process of osteointegration of the dental implant (13) or as the main surface treatment of the implant (24). Traditional titanium dental implant has the heavily discussed titanium oxide outer layer for osseointegration (24). Coatings of the outer layer of the titanium implant were developed to stimulate the process of osteogenesis and increase the bone formation around the implant layer to achieve osseointegration (2). The HA-treated dental implant has an aqueous organic biomolecular interface that is in contact with the human tissue with a hydrated, soft, and primarily distributed throughout the coated areas (24). Moreover, HA can be used as a carrier for antibiotics and used in the coating of titanium implants safely in another in vitro study (25), or as a carrier for rhBMP-2 and coated to the implant interface (26).

**Treatment after implant insertion**

HA can be incorporated for treatment after dental implant insertion. It can reduce the healing time by topical administration of HA gel to the site (27, 28, 29, 30). The topical administration can reduce the load of peri-implantitis related microbial (30), reduce inflammation (29), or have a similar healing effect when compared with chlorhexidine (28).

HA was used together with chlorhexidine mouthwash after implant surgery, giving an anti-edema effect without additional antiplaque effect (31). Dehiscence was also experimented with where HA was included in the allograft and had an overall similar effect to conventional treatment (32). HA was also tested to be used in the treatment of implant mucositis and peri-implantitis in spray form (33, 34). However, due to the small sample size of only five patients recruited in the studies, the outcome might not be conclusive enough.

The overall results from treatment after dental implant placement showed that hyaluronic acid is at least as effective as the conventional treatments that have been
used before. Statistically speaking, there are some benefits from HA groups for treatment after implant insertion when compared to control group such as reduced bleeding index (28), reduced edema two days post-operatively (31), reduced abundance of implantitis-related microorganisms (30), reduced healing time (27), and lower probing depth (29).

**Bone graft/ sinus lift**

Bone graft procedure is commonly used in cases with reduced vertical and horizontal dimensions of bone that are intended for dental implant treatment, especially in the posterior maxilla, at the sinus area (35). In this article, there are several ways that HA was used for bone graft material and sinus lift procedures. HA was mixed with bone graft material in several studies, with a particular interest in the maxillary sinus lift procedure (35, 36, 37, 38, 39). The use of HA added with the bone graft showed improved bone formation (39). Anorganic bovine bone matrix with sodium hyaluronan carrier showed accelerated bone formation and can be effectively used as a DFDBA carrier and improving its handling property (37). Incorporating HA in the bone graft/ sinus lift procedure able to shorten the healing period from six to eight months to just four months (39). PepGen P-15 Putty containing HA carrier was found to have accelerated healing time than another type of bone graft material. Implants were usually placed 9 months after the sinus lift procedure and utilizing PepGen P-15 putty and Hyaloss Matrix can reduce the time to only two to four months (35, 39, 40). Apart from the shorter healing time, addition of graft material with HA was also reported to have better handling to ease the filling of the maxillary sinus area (36, 37, 39). Another commercially available HA, Hyaloss Matrix was examined as a space maintainer in sinus lift procedure and combined with collagenated bone graft material (39, 41). Another more recent study showed that there is no difference of outcome from addition of HA in bone graft material (38). The findings from this category showed that the addition of HA can be used in the bone graft material and sinus lift procedures and showed accelerated bone growth, better handling for the material, and shorten the period before inserting a dental implant, but mostly did not show any statistically significant difference. However, only one study in this category showed statistically significant result for HA group when compared to control group, that is increased bone formation with HA-based matrix in sinus lift procedure (39).

In this review, we have seen some limitations from the articles included where studies include small sample size, short review period, and lack of standardization of the formulation of HA as well as heterogenous methodology, making a meta-analysis not possible. There were four studies that have a sample size of less than ten patients, and four studies had the methodology of review of less than one month period. Only six articles showed statistically significant result in favor of use of HA when compared to the conventional treatment. However, the general findings are that HA groups are at par with the current conventional treatment.

The results of this review revealed that HA has been explored to be incorporated on the dental implant surface, treated after dental implant placement, and incorporated safely in sinus lift/ bone graft material. As suggested by Al-Khateeb et al., a systematic way to report the use of HA in the field of dentistry should be adopted by future researchers (6). Tests of different formulations of HA products to treat the same conditions should also be considered to assist clinicians in selecting the best treatment options.

**CONCLUSION**

This review summarized the possible applications of HA involving dental implant procedures in human clinical studies. It has the potential to be used as implant coating material, bone graft or membrane material, or for treatment after implant insertion Even though the findings of most experimental results are not significantly different from the current standards in some of the studies, showing that HA is safe to be used, and open for further investigations. There are some added benefits with statistically significant results like reduced bleeding, reduced edema, reduced bacterial load, reduced healing time, reduced probing depth, and increased bone formation. However, the limitations in this review include limited number of studies, heterogenicity of the methodology, intervention and analysis used.

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