SYSTEMATIC REVIEW

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

Nur Imanina Abdullah Thaidi[1], Ahmad Badruddin Ghazali[2], Murni Halim[1]

[1] Faculty of Biotechnology and Biomolecular Sciences, Universiti Putra Malaysia, 43400, Serdang, Selangor
[2] Kulliyyah of Dentistry, International Islamic University Malaysia, Bandar Indera Mahkota, 25200, Kuantan, Pahang.

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.
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Corresponding Author:
Ahmad Badruddin Ghazali, MSc (OMFR)
Email: badruddinghazali@iium.edu.my
Tel: +609-5705466

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 Brenemark'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 ($C_{14}H_{21}NO_{11}$)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 zooepidemicus 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

designs included 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.

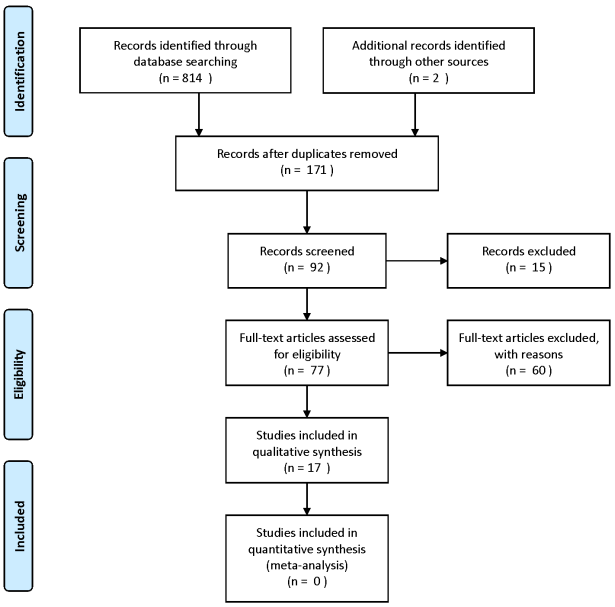

Figure 1: Sample size. Sample size of this study is determined by G*Power.

Table I: Applications of HA in dental implant

Author/ Year	Study type	Study method	Characteristic of intervention	Analysis done	Outcome/ Key Findings
Implant surface treatment					
Lupi et al., 2019 (22)	RCT	Implants treated with the covalently linked hyaluronan implant surface, 52 cases, and 48 control implants for 36 months	Implant fixture coated by covalently-linked HY by Nobil Bio Ricerche	Intraoral periapical radiograph	The implant is successful. No differences were observed in terms of insertion and stability, wound healing, implant success, and crestal bone resorption at any time considered. All interventions had optimal healing, and no adverse events were recorded. The HA-coated dental implant is regarded as successful to be used.
Treatment after implant insertion					
de Araujo Nobre at al., 2007 (23)	RCT	30 edentulous patients, four implants each. post-implant placement HA and CHX gel therapy for six months	0.2% HA gel (Gengigel). Participants used toothbrushes and HA gel application	mBI, mPII, PD, suppuration, mobility	No suppuration or mobility was found in both groups. Statistically significant mBI for HA group. HA is recommended for the first two months while CHX is used between two to six months.
Lopez et al., 2017 (24)	non RCT	Five mucositis patients with implants on different sides. Scaling & root planning on all sides and administered nebulized HA via Spraysol on one side for 15 days	Nebulized HA application via Spray-sol	Tartar Index, Plaque Index, BOP, Pocket Depth	No difference in pocket depth, but improved bleeding on probing no difference in other parameters.
Lopez et al., 2017 (25)	non RCT	Five implantitis patients with implants on different sides. Scaling & root planning on all sides and administered nebulized HA via Spraysol on one side for 15 days	Nebulized HA application via Spray-sol	Tartar Index, Plaque Index, BOP, Pocket Depth	Some improvement in pocket depth, and bleeding on probing, but no statistically significant results.
Genovesi et al., 2017 (26)	RCT	40 patients post-implant surgery, two groups of 0.12%Chx+ 0.1%HA or only 0.12% Chx mouthwash, review after 15 days.	0.1% Aftamed hyaluronic acid added in 0.12% chlorhexidine mouthwash	Surgical outcome variables and plaque, gingival, and staining indexes	Additional anti-edema effect for CHX+HA group. No additional antiplaque or antigingivitic effect for HA.HA can be added to CHX.
Trombelli et al., 2018 (27)	RCT	Post-flap surgery includes implant placement and other procedures. 35 patients. 0.2% Chx and 0.2%Chx+ 0.2%HA+ADS mouth rinse for 21 days	0.2% CHX + 0.2% HA + ADS mouthrinse.	GHI, plaque, tooth discoloration	Optimal Gingival Healing Index, low plaque, gingival inflammation, and staining were observed in both groups. No statistical difference was seen between the two groups. HA did not significantly influence the quality of gingival healing and the levels of plaque and gingival inflammation, both groups healed well.
Kaya et al., 2019 (28)	non RCT	42 cases of class I dehiscence defect treated with HA plus xenograft plus collagen membrane (HAXC) or xenograft plus collagen membrane (XC). Review up to 12 months.	Hydrated HA with saline to get gel consistency and mixed with xenograft particle	CBCT	HAXC reported higher VBH after 6 months. But overall, HA did not have a significant positive effect on the repair of defects around dental implants. Easy handling with HA group compared to xenograft alone.

Table I: Applications of HA in dental implant (continued)

Author/ Year	Study type	Study method	Characteristic of intervention	Analysis done	Outcome/ Key Findings
Soriano-Lerma et al., 2019 (29)	RCT	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.	application by syringe of 0.8% HMW-HA gel	16S rRNA sequencing techniques	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.
Capodiferro et al., 2020 (30)	non RCT	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.	Aminogam gel containing sodium hyaluronate and four synthetic amino acids (glycine, leucine, proline, lysine)	Histological	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.
S6nchez-Fern6ndez et al., 2021 (31)	RCT	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.	0.8% HMW-HA gel	Clinical periodontal variables and marginal bone loss, IL-1β and TNF-α levels in the crevicular fluid.	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.
Bone graft/sinus lift					
Schwartz et al., 2007 (32)	non RCT	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.	DBX hyaluronic acid carrier is used in several DFDBA formulations for sinus graft material.	CT and histomorphometric	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.
Butz et al., 2011 (33)	non RCT	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.	PepGen P-15 Putty, a combination of bovine hydroxyapatite and synthetic peptide in a sodium hyaluronate carrier	MicroCT and Histomorphometric	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.
Emam et al., 2015 (34)	non RCT	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.	PepGen P-15 Putty comprises anorganic bovine bone matrix (ABM) coupled with a synthetic cell-binding peptide, suspended in a sodium hyaluronate carrier.	micro CT and Histomorphometric	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.
Gocmen et al., 2016 (35)	non RCT	Ten patients, one side of sinus lift with HA, while another side with an ultrasonic resorbable pin, reviewed after 6 months.	Hyaloss Matrix applied as space maintenance in the sinus.	CBCT: alveolar bone height and reduction in sinus volume	Sufficient bone height for both techniques, but better results in the resorbable pin group. The dental implant was successfully placed after 6 months.
Knabe et al., 2017 (36)	non RCT	TCP-G (pure) and TCP-P (recombinant sodium hyaluronate powder) are both added with autogenous bone chips for a sinus lift. Total Seven patients. Each type is used in one side of the sinus lift procedure. The sample was taken after 6 months.	pure -TCP granules embedded in a fermented sodium HyAc hydrogel matrix.	CBCT, Histomorphometry, and Immunohistochemistry	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 HyAc. More superior handling, greater bone formation.
Dogan et al., 2017 (37)	RCT	13 patients requiring both sides of sinus augmentation, one side with HA and collagenated bone graft, the other with only collagenated bone graft. Review after 4 months.	hyaluronic matrix (Hyaloss matrix) in addition to CHBG (1 g). Hyaloss is solid in the form of fibers that form a gel when hydrated, releasing pure hyaluronic acid.	MicroCT and histomorphometric	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.
Velasco-Ortega et al., 2021 (38)	RCT	24 patients, receiving either anorganic bovine bone mineral as control, tricalcium phosphate with or without hyaluronic acid (HA), review after 9 months.	TCP plus crosslinked HA (Hyadent BG)	histomorphometric analysis, mean bone gain, intraoperative and post-operative complications, implant insertion torque, implant failure, and patient-reported outcome measures	The addition of HA did not influence the outcomes, with non-significant findings. An implant placed after 9 months.

Table II: Risk of bias assessment

Lupi et al., 2019	de Araujo Nobre at al., 2007	Lopez et al., 2017 mucositis	Lopez et al., 2017 implantitis	Genovesi et al., 2017	Trombelli et al., 2018	Kaya et al., 2019	Soriano-Lerma et al., 2019	Capodiferro et al., 2020	Sõnchez-Fernõndez et al., 2021	Schwartz et al., 2007	Butz et al., 2011	Emam et al., 2015	Gocmen et al., 2016	Knabe et al., 2017	Dogan et al., 2017	Velasco-Ortega et al., 2021	
(+)	(+)	(-)	(-)	(+)	(+)	(?)	(+)	(?)	(+)	(-)	(-)	(-)	(?)	(-)	(+)	(+)	Random sequence generation (selection bias)
(+)	(+)	(-)	(-)	(?)	(+)	(-)	(+)	(?)	(+)	(-)	(-)	(-)	(-)	(-)	(?)	(?)	Allocation concealment (selection bias)
(+)	(+)	(-)	(-)	(+)	(+)	(?)	(+)	(-)	(+)	(-)	(-)	(-)	(-)	(-)	(?)	(?)	Blinding of participants and personnel (performance bias)
(?)	(?)	(-)	(-)	(+)	(+)	(-)	(+)	(-)	(+)	(-)	(-)	(-)	(-)	(-)	(?)	(?)	Blinding of outcome assessment (detection bias)
(+)	(+)	(?)	(?)	(+)	(+)	(?)	(+)	(?)	(+)	(?)	(?)	(?)	(-)	(?)	(+)	(+)	Incomplete outcome data (attrition bias)
(+)	(+)	(?)	(?)	(+)	(+)	(?)	(+)	(?)	(+)	(?)	(?)	(?)	(?)	(?)	(+)	(+)	Selective reporting (reporting bias)
(+)	(+)	(?)	(?)	(+)	(+)	(?)	(+)	(?)	(+)	(?)	(?)	(?)	(?)	(?)	(+)	(+)	Other bias

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 authours have coated the titanium implant with HA from Nobil 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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REFERENCES

1. Clark D, Levin L. In the dental implant era, why do we still bother saving teeth? Dent Traumatol. 2019;35(6):368-75. doi: 10.1111/edt.12492.
2. Kellesarian SV, Malignaggi VR, Kellesarian TV, Bashir Ahmed H, Javed F. Does incorporating collagen and chondroitin sulfate matrix in implant surfaces enhance osseointegration? A systematic review and meta-analysis. Int J Oral Maxillofac Surg. 2018;47(2):241-51. doi: 10.1016/j.ijom.2017.10.010.
3. Block MS. Dental Implants: The Last 100 Years. J Oral Maxillofac Surg. 2018;76(1):11-26. doi: 10.1016/j.joms.2017.08.045.
4. Buser D, Sennerby L, De Bruyn H. Modern implant dentistry based on osseointegration: 50 years of progress, current trends and open questions. Periodontol 2000. 2017;73(1):7-21. doi: 10.1111/

prd.12185.
5. Griggs JA. Dental Implants. Dent Clin North Am. 2017;61(4):857-71. doi: 10.1016/j.cden.2017.06.007.
6. Al-Khateeb R, Olszewska-Czyz I. Biological molecules in dental applications: hyaluronic acid as a companion biomaterial for diverse dental applications. Heliyon. 2020;6(4):e03722. doi: 10.1016/j.heliyon.2020.e03722.
7. Bukhari SNA, Roswandi NL, Waqas M, Habib H, Hussain F, Khan S, et al. Hyaluronic acid, a promising skin rejuvenating biomedicine: A review of recent updates and pre-clinical and clinical investigations on cosmetic and nutricosmetic effects. Int J Biol Macromol. 2018;120(Pt B):1682-95. doi: 10.1016/j.ijbiomac.2018.09.188.
8. Abdullah Thaidi NI, Mohamad R, Wasoh H, Kapri MR, Ghazali AB, Tan JS, et al. Development of In Situ Product Recovery (ISPR) System Using Amberlite IRA67 for Enhanced Biosynthesis of Hyaluronic Acid by Streptococcus zooepidemicus. Life. 2023;13(2):558. doi: 10.3390/life13020558.
9. Zhai P, Peng X, Li B, Liu Y, Sun H, Li X. The application of hyaluronic acid in bone regeneration. Int J Biol Macromol. 2020;151:1224-39. doi: 10.1016/j.ijbiomac.2019.10.169.
10. Shuborna NS, Chaiyasamut T, Sakdajeyont W, Vorakulpipat C, Rojvanakarn M, Wongsirichat N. Generation of novel hyaluronic acid biomaterials for study of pain in third molar intervention: a review. J Dent Anesth Pain Med. 2019;19(1):11-9. doi: 10.17245/jdapm.2019.19.1.11.
11. Neuman MG, Nanau RM, Oruca-Sanchez L, Coto G. Hyaluronic acid and wound healing. J Pharm Pharm Sci. 2015;18(1):53-60. doi: 10.18433/j3k89d.
12. Casale M, Moffa A, Vella P, Sabatino L, Capuano F, Salvinelli B, et al. Hyaluronic acid: Perspectives in dentistry. A systematic review. Int J Immunopathol Pharmacol. 2016;29(4):572-82. doi: 10.1177/0394632016652906.
13. Yazan M, Kocyigit ID, Atil F, Tekin U, Gonen ZB, Onder ME. Effect of hyaluronic acid on the osseointegration of dental implants. The British journal of oral & maxillofacial surgery. 2019;57(1):53-7. doi: 10.1016/j.bjoms.2018.08.014
14. Boeriu CG, Springer J, Kooy FK, van den Broek LAM, Eggink G. Production Methods for Hyaluronan. International Journal of Carbohydrate Chemistry. 2013;2013:624967. doi: 10.1155/2013/624967
15. Schanté CE, Zuber G, Herlin C, Vandamme TF. Chemical modifications of hyaluronic acid for the synthesis of derivatives for a broad range of biomedical applications. Carbohydrate Polymers. 2011;85(3):469-89. doi: 10.1016/j.carbpol.2011.03.019
16. Johansson B, Smedberg JI, Langley M, Embery G. Glycosaminoglycans in peri-implant sulcus fluid from implants placed in sinus-inlay bone grafts. Clin Oral Implants Res. 2001;12(3):202-6. doi: 10.1034/j.1600-0501.2001.012003202.x.
17. Smedberg JI, Beck CB, Embery G. Glycosaminoglycans in peri-implant sulcus fluid from implants supporting fixed or removable prostheses. Clin Oral Implants Res. 1993;4(3):137-43. doi: 10.1034/j.1600-0501.1993.040304.x.
18. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gωtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700. doi: 10.1136/bmj.b2700.
19. Mohamed Shaffril HA, Samsuddin SF, Abu Samah A. The ABC of systematic literature review: the basic methodological guidance for beginners. Quality & Quantity. 2021;55(4):1319-46. doi: 10.1007/s11135-020-01059-6
20. Group OLoEW. The Oxford Levels of Evidence 2, Oxford Centre for Evidence-Based Medicine. [Available from: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence.
21. Higgins JPT, Altman DG, Gøtzsche PC, Jьni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928. doi: 10.1136/bmj.d5928.
22. Ahmadian E, Dizaj SM, Eftekhari A, Dalir E, Vahedi P, Hasanzadeh A, et al. The Potential Applications of Hyaluronic Acid Hydrogels in Biomedicine. Drug Res (Stuttg). 2020;70(1):6-11. doi: 10.1055/a-0991-7585.
23. Koray M, Ofluoglu D, A S, Issever H, Yaltirik M. The Efficacy of Hyaluronic Acid Gel in Pain Control of Recurrent Aphthous Stomatitis. International Journal of Dentistry and Oral Science. 2016:273-5. doi: 10.19070/2377-8075-1600055
24. Lupi SM, Rodriguez YBA, Cassinelli C, Iviglia G, Tallarico M, Morra M, et al. Covalently-Linked Hyaluronan versus Acid Etched Titanium Dental Implants: A Crossover RCT in Humans. Int J Mol Sci. 2019;20(3). doi: 10.3390/ijms20030763.
25. Boot W, Gawlitta D, Nikkels PGJ, Pouran B, van Rijen MHP, Dhert WJA, et al. Hyaluronic Acid-Based Hydrogel Coating Does Not Affect Bone Apposition at the Implant Surface in a Rabbit Model. Clin Orthop Relat Res. 2017;475(7):1911-9. doi: 10.1007/s11999-017-5310-0.
26. Pan H, Han JJ, Park YD, Cho TH, Hwang SJ. Effect of sustained release of rhBMP-2 from dried and wet hyaluronic acid hydrogel carriers compared with direct dip coating of rhBMP-2 on peri-implant osteogenesis of dental implants in canine mandibles. J Craniomaxillofac Surg. 2016;44(2):116-25. doi: 10.1016/j.jcms.2015.11.018.
27. Capodiferro S, Tempesta A, Bucci S, Maiorano E, Favia G, Limongelli L. Aminogam® Gel Allows

Faster Wound Healing after Oral Surgery by Formation of Mature Connective Tissue with Low Vascular Density and Reducing Inflammatory Infiltration. A Retrospective Study on 580 Cases with Histological and Confocal Laser Investigation. Applied Sciences. 2020;10(3):1105. doi: 10.3390/app10031105

28. de Araújo Nobre M, Cintra N, Maly P. Peri-implant maintenance of immediate function implants: a pilot study comparing hyaluronic acid and chlorhexidine. Int J Dent Hyg. 2007;5(2):87-94. doi: 10.1111/j.1601-5037.2007.00239.x.
29. Sánchez-Fernández E, Magán-Fernández A, O'Valle F, Bravo M, Mesa F. Hyaluronic acid reduces inflammation and crevicular fluid IL-1β concentrations in peri-implantitis: a randomized controlled clinical trial. J Periodontal Implant Sci. 2021;51(1):63-74. doi: 10.5051/jpis.1903660183.
30. Soriano-Lerma A, Magán-Fernández A, Gijyn J, Sánchez-Fernández E, Soriano M, García-Salcedo JA, et al. Short-term effects of hyaluronic acid on the subgingival microbiome in peri-implantitis: A randomized controlled clinical trial. J Periodontol. 2020;91(6):734-45. doi: 10.1002/JPER.19-0184.
31. Genovesi A, Barone A, Toti P, Covani U. The efficacy of 0.12% chlorhexidine versus 0.12% chlorhexidine plus hyaluronic acid mouthwash on healing of submerged single implant insertion areas: a short-term randomized controlled clinical trial. Int J Dent Hyg. 2017;15(1):65-72. doi: 10.1111/idh.12158.
32. Kaya OA, Muglali M, Torul D, Kaya I. Peri-implant bone defects: A 1-year follow-up comparative study of use of hyaluronic acid and xenografts. Niger J Clin Pract. 2019;22(10):1388-95. doi: 10.4103/njcp.njcp_502_18
33. Lopez MA, Manzulli N, D'Angelo A, Candotto V, Casale M, Lauritano D. The use of hyaluronic acid as an adjuvant in the management of mucositis. J Biol Regul Homeost Agents. 2017;31(4 Suppl 2):115-8.
34. Lopez MA, Manzulli N, D'Angelo A, Lauritano D, Papalia R, Candotto V. The use of hyaluronic acid as an adjuvant in the management of peri-implantitis. J Biol Regul Homeost Agents. 2017;31(4 Suppl 2):123-7.
35. Butz F, Bächle M, Ofer M, Marquardt K, Kohal RJ. Sinus augmentation with bovine hydroxyapatite/synthetic peptide in a sodium hyaluronate carrier (PepGen P-15 Putty): a clinical investigation of different healing times. Int J Oral Maxillofac Implants. 2011;26(6):1317-23.
36. Knabe C, Adel-Khattab D, Kluk E, Struck R, Stiller M. Effect of a Particulate and a Putty-Like Tricalcium Phosphate-Based Bone-grafting Material on Bone Formation, Volume Stability and Osteogenic Marker Expression after Bilateral Sinus Floor Augmentation in Humans. J Funct Biomater. 2017;8(3). doi: 10.3390/jfb8030031.
37. Schwartz Z, Goldstein M, Raviv E, Hirsch A, Ranly DM, Boyan BD. Clinical evaluation of demineralized bone allograft in a hyaluronic acid carrier for sinus lift augmentation in humans: a computed tomography and histomorphometric study. Clin Oral Implants Res. 2007;18(2):204-11. doi: 10.1111/j.1600-0501.2006.01303.x
38. Velasco-Ortega E, Valente NA, Iezzi G, Petrini M, Derchi G, Barone A. Maxillary sinus augmentation with three different biomaterials: Histological, histomorphometric, clinical, and patient-reported outcomes from a randomized controlled trial. Clin Implant Dent Relat Res. 2021;23(1):86-95. doi: 10.1111/cid.12964.
39. Dogan E, Dursun E, Tosun E, Bilgic E, Akman AC, Orhan K, et al. Evaluation of hyaluronic matrix efficacy in sinus augmentation: a randomized-controlled histomorphometric and micro-computed tomography analysis. Int J Oral Maxillofac Surg. 2017;46(7):931-7. doi: 10.1016/j.ijom.2017.03.003.
40. Emam HA, Behiri G, El-Alaily M, Sharawy M. The efficacy of a tissue-engineered xenograft in conjunction with sodium hyaluronate carrier in maxillary sinus augmentation: a clinical study. Int J Oral Maxillofac Surg. 2015;44(10):1287-94. doi: 10.1016/j.ijom.2015.04.011.
41. Gцçmen G, Atalı O, Aktop S, Sipahi A, Gцnьl O. Hyaluronic Acid Versus Ultrasonic Resorbable Pin Fixation for Space Maintenance in Non-Grafted Sinus Lifting. J Oral Maxillofac Surg. 2016;74(3):497-504. doi: 10.1016/j.joms.2015.10.024.