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RESEARCH ARTICLE

ROLE OF HYALURONIC ACID IN PERIODONTAL BONE REGENERATION

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Abstract

Hyaluronic acid is a natural component of extra cellular matrix in both soft and hard periodontal tissues .Hyaluronic acid is located in both mineralised tissues (i.e cementum and alveolar bone) and non mineralised tissues (i.e gingiva and periodontal ligament) .Hyaluronic acid due to its anti-inflammatory ,anti -edematous ,anti- bacterial ,stimulation of angiogenic effects and osteoconductive effects has the potential to regulate periodontal tissue regeneration .Along with these properties , its role in modulation of wound healing makes it an adjunct to surgical and non surgical periodontal therapy.The use of Hyaluronic acid to treat periodontal bone defects has been shown to accelerate bone regeneration owing to its osteoconductive potential ,proliferation and differentiation of mesenchymal cells ,and regulating activities of osteoblast ,fibroblast ,cementoblast along with enhancement of osteogenetic effect of bone morphogenetic protein -2 in periodontal regeneration .This review examines the current literature favouring the use of hyaluronic acid in the regeneration of periodontal infrabony defects.

Introduction:

Periodontitis is a chronic inflammatory disease that is brought on by host bacterial interaction[1.] Periodontal bone defects make periodontal therapy necessary and should primarily focus on regeneration of injured tissues [2.] Regeneration intends to replace the damaged bone with new alveolar bone, periodontal ligament, and cementum, restoring the entire periodontal complex.

Very recently, Nibali et al.2021, pointed out that periodontal regenerative procedures should be the treatment of choice for intrabony defects with the depth, angle, and number of walls affecting both clinical and radiological outcomes.[3] Conventional periodontal regeneration approaches with guided tissue regeneration (GTR) membrane [4] enamel matrix derivatives [5],guided bone regeneration (GBR), with or without root conditioning has resulted only in some degree of success.[6]

Currently biomaterials like Hyaluronic acid (HA) for treating, intra-bony periodontal defectsbeen reported due to its distinct biological functions as well as unique physicochemical properties (hygroscopicity and viscoelasticity)[7]

History:

The term "hyaluronic acid" (a popular term derived from "hyalos," which is the Greek word for glass + uronic acid). In 1934, Karl Meyer and his colleague John Palmer isolated a hitherto unknown chemical substance from the

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vitreous body of cows' eyes.Endre Balazs is credited with coining the term "hyaluronan," which was first used in 1986 to comply with the international nomenclature of polysaccharides [8]

Structure,Biosynthesis and Degradation:
HA is a non-sulfated glycosaminoglycan (GAG) composed of repeating disaccharide units in linear chain linked by β-1,4-glycosidic bonds. N-acetyl-dglucosamine and D-glucuronic acid are present in each disaccharide unit, linked by β 1,3-glycosidic bond.[9]

In the periodontal tissues, HA is synthesized by HA synthase enzymes (HAS -1,2,3) that are found in a variety of cell types, including fibroblasts, cementoblasts, osteoblasts, and periodontal ligament cells[7,10]. The concentration of HA is lower in mineralised tissues (cementum and alveolar bone), compared to non mineralised tissues (gingiva's connective tissue and the periodontal ligament) [10,11]

The content of HA in human gingival epithelium and connective tissue has been calculated to be circa 5.58 μg/g dry wt and circa126.4 μg/g dry wt respectively. In case of inflammation, hyaluronidases, the activity of reactive oxygen and nitrogen species, etc. induce the HA into smaller fragments of different MW [12,13], as evidenced by a shift towards low-molecular size glycosaminoglycans in gingiva of periodontitis patients .[14].

Types of HA
HA on the basis of molecular weight (MW)is classified into Low molecular weight (LMW)and high molecular weight (HMW)HA.Molecular weight of HA determines its biological effects.

HMW -HA (>500 KDa) possesses anti- inflammatory, antiangiogenic (inhibiting endothelial cell migration and proliferation) and immunosuppressing properties with ability to form strong bonds and has more attachment area for CD44 receptor. It enhances mRNA expression of osteogenic gene markers AGP,RUNX2. OCN thereby enhancing osteoinduction and coats cells and covers TLR limiting interaction with ligand.

LMW-HA (0.4 -4 KDa) possesses pro inflammatory effects due to interaction with CD44+, promote angiogenesis (stimulating cell proliferation and migration) and has less ability to form strong bonds and less attachment area for CD44 receptor.Itenhances proliferation of bone marrow derived mesenchymal skin cells and act as agonist for TLR 2 and TLR-4 triggering inflammatory reaction.[10,15,16,17]

Properties:
The hygroscopic and viscoelastic properties of HA confers conformational rigidity via retention of water .Moreover, it is biocompatible, non-immunogenic, bacteriostatic, promotes the synthesis and deposition of collagen increases osteoblasts activity favouring osteogenesis .Also, HA has antiadhesive properties,anti-inflammatory properties and antioxidant properties on reactive oxygen species [15]along with anti-oedematous properties related to osmotic action [16,17]and are mediated by receptor-mediated mechanisms [18,19] .

Proposed Mechanism of Action of Ha in Periodontal Regeneration:
Mechanism of action of HA can be divided into: passive and active mechanism

Passive Mechanism:
It is dependent on the chemical and physical characteristics of HA. Being a natural ECM component, it acts as biomimetic ECM with enhanced cell adhesion, proliferation, and differentiation. [20]

Active Mechanism:
It works by inducing signal transduction pathway by means of ligand binding to its receptors.

Two types receptors of HA :[21]
1. HA binding proteoglycans (extracellular or matrix hyaladherins)
2. HA cell surface receptor (cellular hyaladherins

HA - CD44 Receptor:
It is a surface receptor and main receptor for HA. HA -CD44 interaction increases the release of pro-inflammatory cytokines[18,21,22,23]. Interaction between HA and CD44 will activate the tyrosine kinase receptor pathway [21]and can

regulate cell adhesion and migration [24]. The higher the HA molecular weight, the more attachment areas for the CD44 receptor. [15,16,17]

HA- RHAMM (Receptor for hyaluronan-mediated motility):
RHAMM receptor is expressed in motile cells like fibrocytes and can be found in the cell membrane, cytoplasm, and nucleus. Cell surface RHAMM enhances cell migration when HA is present, while intracellular RHAMM regulates activating various signalling pathways and influencing cells like macrophages and fibroblasts [25]. It activates serine, tyrosine, RAS and src pathways.
CD44 AND RHAMM: Turley et al 2002 in his study on signalling properties of hyaluronan receptors showed that CD44 and RHAMM pathways function by interacting with tyrosine kinases, Rho like GTpases, and some cytoskeleton componenets .[22]

HA -ICAM-1 (Intercellular adhesion molecule -1): HA -ICAM-1 interaction impact on its binding to other receptors, including lymphocyte function associated-1 (LFA-1) and leukocyte integrins [26]

HA - TLR (Toll -like receptors):
TLR - HA interaction contributes to bacteriostatic effect by two potential mechanisms. Firstly, LMW HA activates TLR2 and TLR4, leading to an inflammatory response [21,27]Secondly,HA regulates TLR through its pericellular jelly barrier, rather than binding to them[28].

HA -HARE: (Hyaluronan receptor for endocytosis)
HARE interacts with HA leading to breakdown and removal of HA from blood circulation [28]

HA -LYVE1 (Lymphatic vessel endothelial hyaluronan receptor 1):
These receptors regulate tissue hydration, bond with growth factors, prostaglandins and other tissue mediators regulating lymphangiogenesis and intercellular adhesions .[28]

Beneficial Osteogenetic Effects of HA in Periodontal Regeneration:
The process of bone repair includes hematoma formation, inflammatory phase, granulation tissue,callus formation, and remodeling phase. HA promotes bone regeneration by regulating cell activity and the release of biological factors. [29]

HA as biomimetic scaffold material:
HA provides a natural biomimetic extracellular environment for cell adhesion, proliferation and differentiation via activation of receptors like CD44, ICAM -1 and RHAMM. It can be used as a carrier for osteogenesis related cells and factors like BMP-2 and PDGF-BB **.[30]**

Effect of HA on osteoblast activity:
By direct or indirect CD44 -HA interaction controls activity of osteogenic cells by binding to HA and regulates cell motility by binding to RHAMM. HMW-HA molecules increase the mRNA expressions of osteogenic gene markers (i.e., RUNX-2, ALP, and OCN) low molecular weight isoforms may encourage cell division and proliferation.[31,32]

Effect of HA on fibroblast activity:
HA influence periodontal ligament fibroblast via specific signaling molecules (Akt, Erk1/2, and p38) and cell migration, proliferation as well as triggers the expression of genes TGFB3 and COL3A1, essential for scar-free wound healing. HA influence ECM remodeling activity by inducing the expression of MMP genes (such as MMP1 and 8) and growth factors genes (PDGFB, FGF-2, and EGF) [33]

Effect of HA on cementoblast activity:
In vitro studies have shown that HA treated cementoblast enhance viability and capacity to produce minerals demonstrated by the increased expression of markers for mineralized tissues (COL-I, BSP, RunX2, ALP, and OCN) [34]

Enhancement of Osteogenetic Effect of BMP-2:

The binding of HA to its receptors can activate growth factors like Transforming growth factor-beta (TGF-β) Vascular endothelial growth factor regulating the processes of proliferation, differentiation, migration, and extracellular matrix protein synthesis. Bone morphogenetic protein -2 (BMP-2) a member of TGF-β superfamily,inturn activates SMAD pathway and accelerate bone formation.[35,36.] Research evidence have shown that HAenhances signalling pathway involving smad protein family and suppresses extracellular signal-regulated kinase (ERK) phosphorylation as well as down regulates BMP- 2 antagonist like nogging and follistatin occurs IN MG63 cells under BMP- 2 stimulation.

Angiogenic Effects of HA:

Angiogenic effect is important for osteogenesis [37,38,39]. Fragments of HA enhances angiogenesis via RHAMM mediated signalling pathway in epithelial cells.It also promotes proliferation and migration of Ecs in process of vessel formation [40]. HA stimulates angiogenesis, leading to enhancement of wound healing in the bone matrix. At a low molecular weight, HA is angiogenic, whereas at a high molecular weight, HA is anti-angiogenic[16]

Evidence For Role of HA in Periodontal Bone Regeneration

HA has several favorable characteristics that give it a promising role in alveolar bone regeneration. Literature evidence regarding this has been observed in the included animal studies(Table 1),in vitro (Table 2), human trial (Table 3) and systematic review(Table 4).

Various animal models with various types and concentrations of HA were observed in animal studies and HA was combined with a variety of growth factors to improve its function in furcation defects, intrabony defects, and extraction sockets.Thecombination of HA with other agents improved osteoconductive and osteoinductive properties, resulting in new bone production.The In vitro studies also showed similar results favouring bone regeneration

The beneficial effects of using HA in periodontal infra bony defects were noted by both Engstrom et al 2001 and Florin Onisor et al 2022 with the former studyshowing increase in radiographic bone level at 12 months from baseline [41,42].Systematic review by Eliezer et al also demonstrated beneficial role of HA in PPD reduction ,Cal gain and decrease in BOP in surgical and nonsurgical periodontal therapy.[43]

In a study by Fawzy et al 2012, Briguglio et al 2013, Mamajiwala et al 2021 OFD was done by using MWF technique, simplified papilla preservation, parapapillary incision technique respectively,to access the defect while preserving the interdental papilla and achieve clot stability. Bone gain was assessed in last two studies by radiographic assessment [44,45,46]. Sehdev et al 2016 in his study have noticed greater improvement in radiographic defect depth in intrabony defects when HA +Bioresorbable degradable membrane was used .[47]

An RCT by Pillioni et al 2002 used single-flap approach (SFA) along with HA or enamel matrix derivative (EMD) in treating intrabony defects and noticed that application of EMD showed significant CAL gain and reduction in PD than HA .[48]An RCT by Santana et al 2015 showed radiographic bone gain in periodontal intrabony defects when HA was combined with recombinant human Fibroblast Growth Factor type 2 (rhFGF-2) [49].Similar results were noticed in many animal and invitro studies.Contradictorily 1% HA when used in extraction sockets promoted bone formation in dogs [50]

In a systematic review by Rodríguez-Aranda M et al 2022 has demonstrated improvement in CAL,PPD,BOP and radiographic parameters when HA was used alone or in combination with other biomaterials [51]. Two clinical reports by Ballini et al 2009 and Bozic et al 2021 found that when HA with Autologous /Xenogenic bone graft resulted in significant improvement of CAL gain while Ballini observed infra bone filling in one to three walled infrabony defect. [52,53]

In the view of above studies HA with its osteoconductive and osteoinductive properties promote bone regeneration in infrabony defects. Although HA products with varying concentrations were used most of the studies showedvagueness in their mention. Few studies focused on LMW HA and no radiographic evaluation of bone regeneration was performed in most studies. Our review also observed that the mechanism by which HA exerted its osteogenic effects are rarely stated in many of the studies.

Conclusion:

Our review concluded that HA as stand alone or combined approach with bone graft,barriermembrane, EMD Growth factors has the potential for bone regeneration and PPD reduction when used as a treatment option for deep intrabony defects. However,due to heterogenicity among studies this data should be accounted for with caution.

Future Perspectives:

HA and its derivatives have been used to create HA-based biomaterials with nanoparticles and nanofibers for bone regeneration. To increase bioactivity, and enzymatic stability and mechanical strength HA and its derivatives can be chemically modified.Hybrid scaffold based on HA with varying physiochemical properties can be created and employed to repair various bone tissue components and stimulate bone regeneration.HA and derivatives currently used as a carrier for numerous osteogenesis-related cells and growth factors.The recent fabrication techniques based on 3D printing technology has opened up a new field of personalised HA-based biomaterial construction. As tissue engineering based biomaterials and recent advancement in fabrication methods can lead to more intelligent and complex HA based scaffolds- that are likely to emerge as novel bone regeneration options.[54]

Table 1: Animal studies implicating the role of HA in periodontal regeneration.

Author (year)	Type of study and duration	Sample size	HA form / Commerical product (if any mentioned in the study)	Intervention	Conclusion of the study
Tella et al 2023	RCT Split mouth design 3 months	8 beagle dogs	0.8% HA gel (Gengigel)	Class II furcation defects 0.8% HA gel + Acellular dermal matrix allograft (ADMA) 0.8% HA gel only	HA with ADMA positively affects the periodontal regeneration and wound healing in class II furcation defects
Shirakata et al 2021	Experimental study 2 months	6 BeagleDogs	Cross – linked HA gel (Hyadent BG)	two-wall intrabony defects Open flap debridement (OFD) + HA OFD +CM (Fibro-Gide), OFD + HA +CM	Periodontal regeneration evidenced through the formation of cementum, periodontal ligament and bone
Jung -Ju Kim et al 2019	Experimental study 3 months	6 beagle dogs	1% HA gel + Absorable collagen sponge,Absorable collagen sponge +rhBMP -2	Extraction sockets	HA can promote bone formation and improve wound healing rate
Arpag et al 2017 (1st study compare HA with Xenograft)	Experimental study	Rabbits	HMWHA +Xenograft (Orthovisc)	Calvarial bone	HMW-HA could improve the healing of xenograft by formation of new bone.
Jung -Ju Kim et al 2016	Pilot study 7 months	6 beagle dogs	1% HA gel	Extraction sockets	Ha due to its osteoinductive bacteriostatic and antiinflammatory properties improve bone formation and accelerate wound healing in infected

					sockets
Segari et al 2014	Experimental study	12 Dogs	Ester HA gel mixed with beta tricalcium phosphate	Peripaical lesions	Osteoid bone trabeculae were formed and mature dense bone present at the periphery of cavity site
Suzuki et al 2014	Experimental study	Mouse	Na HA	Calvaria Subperiosteal region	Osteoconductive property of OCP was accelerated by the HA –
Lee et al 2014	Experimental study	17 RabbitS	HA – based powder gel + BMP-2, Beta tricalcium phosphate	Tibia	HA with rhBMP-2 powder gel composite improved osseointegration of the dental implant by increasing the amount of newbone formation in the implant pitch
Ryo Jimbo et al 2014	Experimental study	Non human primate (Macaca Fascicularis)	HMW-HA	Class III furcation defect (HMW + Brain-Derived Neurotrophic Factor (BDNF)	use of BDNF in combination with HMw hyaluronic acid scaffold in class III furcation defects has promoted regenerationofalveolar bone
Bae et al 2014	Experimental study	Rabbit	HA gel +GDF-5	Cranium	HA based hydrogels has a significant improvementonosteogenesis
Kisiel et al 2013	Experimental study	Rat	Injectable Hydrogel (16mg / ml) +BMP-2	Subperiosteumcarnial	Significant bone growth when used in injectable form
Hulsart – Billstrom et al 2013	Experimental study	Rat	Cross linked HA +BMP -2 and hydroxyapatite	Subcutaneous region	Solid hydrogels induced bone formation of a dense bone shellCrushed hydrogels demonstrated a uniform bone formation
Martinez Sanz et al 2012	Experimental study	28 Rat	HA gel + BMP2 Nanohydroxyapapetite	hemimandibles	Significant increase in mandibular bone volume
Bae et al 2011	Experimental study	Rabbit	high molecular weight HA gel + Simvastatin	Cranium	HA hydrogel loaded with 1mg of simvastatin had a significant influence on osteogenesis
Kang et al 2011	Experimental study	6weeks old mice	Multi head deposition system coated with fibrin and HA +BMP-2 and ASCs	Subcutaneous region	BMP-2 loaded Fibrin and HA coating of scaffold significantly enhancedinitial cell attachment and stimulates bone regeneration
Patterson et al 2010	Experimental study	Rat	Cross – linked HA gel + BMP-2 or VEGF	Calvaria	Osteoconductive potential when HA combined with BMP-2
Mendes et al 2010	Experimental study	Rat	Sodium hyaluronate - HA	Molar extraction sockets	Sodium hyaluronate -HA accelerates the repair of bone defects
Kim et al	Experiment	Rat	MMP sensitiveHA	Calvaria	Used as scaffolds in bone

2010	al study		based hydrogel +BMP -2 or hMSCs		tissue engineering with improvements on tissue remodelling rates and regeneration
Xu et al 2010	Experimental study	Rat	Bioactive glass -collagen- hyaluronic acid-phosphatidylserineMSCs	Femurs	Bioactive glass -collagen-hyaluronic acid-phosphatidylserineScaffold exhibited a low inflammatory response when compared with MScs scaffold alone
Maus at al 2008	Experimental study	Sheep	Injectable HA + bmp-2 (Hyalart)	Femora	Lack of bone formation inside the defects
Docherty-S kogh et al 2008	Experimental study	14 Minipigs	5 ml of Hydrogel with 1.25 mg of BMP-2	Calvaria	Injectable hydrogel may be favourable as a BMP-2 carrier for bonereconstructionand resulted in complete healing of the defects
Lisignoli et al 2002	Experimental study	Rat	HA – based polymer scaffold, HA – based polymer scaffold + BMSCs +bFGF	Radius	Mineralisation of bone defects occurred in the presence of HA based polymer scaffold
Sasaki et al 1995	Experimental study 2 WEEKS	10 weeks old rats	High MW	Cortical bone from rat femur	new bone formation By HMW HA Evidenced through mesenchymal cell differentiation in bone wounds.

Table 2: In- vitro studies implicating the role of HA in periodontal regeneration.

Author (year)	**Type of study and duration**	**Sample**	**HA form / Commerical product (if any mentioned in the study)**	**Incorporated Cells/ Growth Factors**	**Conclusion of the study**
Frashier et al 2023	Invitro	Immortalized human PDL cells (PDL - hTERT)	HMW (>950kDa) LMW(75–350kDa) MMW (15–40kDa) ULMW (4–8kDa)	n immortalized periodontal ligament cells (PDLhTERT	hyaluronan can promote metabolic activity and mineralization of PDL-hTERT cells, with LMW HA being the most efective.
Kobayashi,et al 2017	Invitro	Human PDL cells	(HA_ncl)-Non crosslinked hyaDENT or (HA_cl) – Crosslinked hyaDENT BG 2 different concentrations of 1:10 and 1:100	-	Diluted HA_ncl and HA_cl significantly increased PDL cell viability, increased proliferation, and early osteogenic differentiation but was associated with a significant decrease in late osteogenic differentiation of

			dilutions		primary human PDL cells.
Ningbo Zhao et al 2015	Invitro	Rabbit bone marrow msc	0.5%,1% and 2% HA	Rabbit bone marrow-derived stem cells (rBMSCs) + HA, rBMSCs	High MW HA decreases cell adhesion. Cell proliferation was enhanced by low MW HA
Kaneko et al 2015	Invitro	cartilage,	900–1200 0; 0.05; 0.5; 1 mg/Ml HA	-	CD44-blocking antibody restored HA-induced inhibition of osteoblastic differentiation and Smad1/Smad5/Smad8 phosphorylation
Diego G. Miranda et al 2015	Invitro	CS-HA hydrogel scaffolds	modified hyaluronic acid (HA) and chitosan (CS)	SCAFFOLD	CS-HA hydrogel scaffolds was tested using NIH3T3 and MG63 cell lines. It showed a significant increase in cellular viability and high CD44 expression
Katsuhiro Takeda et al 2011	Invitro	Human PDL cells	HMW-HA	**I.** BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF	A greater volume of newly formed alveolar bone and a longer newly formed cementum were observed in (HMW +BDNF) gROUP HMW-HA itself does not enhance periodontal tissue regeneration
Kawano et al 2011 (1st study)	Invitro	osteoblastic lineage MG63	High molecular weight HA (2000 kDa)	osteoblastic lineage MG63 +BMP-2 + HA(100 µg/ ml)	HA when combined with BMP-2 induces osteoblastic differentiation in MG63 cells
Wataru Ariyoshi et al 2005	IN vitro	mouse monocyte cell line (RAW 264.7) mouse monocyte cell line (RAW 264.7) mouse monocyte cell line (RAW 264.7) mouse monocyte cell line (RAW	< 8,000 (low molecular weight HA (LMW-HA) LMW (<8000 kDa) HMW (< 8,000 (low molecular weight HA (LMW-HA) HMW > 900000 kDa	HA (100 g/ml))	LMW-HA plays an important role in osteoclast differentiation and functio n through the interaction of RANKL and RANK than HMW -HA

		264.7) Mouse monpocyte cell line (RAW			

Table 3: Human studies implicating the role of HA in periodontal regeneration.

Author (year)	Type of study and duration	Sample size	HA form / Commerical product (if any mentioned) witn concentration	Intervention with cintrol	Conclusion of the study
Mamajiwala et al 2021	RCT Split mouth 12 months	20	0.8 %HA gel (Gengigel)	One/two-wall Infra-bony defects HA gel +OFD vs OFD + Placebo	HA showed significsntly greater CAL gain and bone defect fill
Bhowmik and Rao et al 2021	Split – mouth design 12 Months	32	HA gel	Infrabonydefcets/ Bilateral vertical defects HA + NHA bone graft (H-NHA) vs NHA alone	H-NHA group showed a greater reduction in PPD and defect depth
Pilloni et al 2021	RCT -Parellel groups 12 months	32	Cross linked and natural 0.2% HA gel (Hyadent)	Interproximal intrabony defects HA gel + SFA vs EMD (Emdogain)+ SFA (Single flap approach)	Statistically significant improvement in PPD Reduction a nd clinical attachment gain
Bozic et al 2021	Clinical report (18 months)	40	Cross linked HA gel (Hyadent BG)	1 to 3-wall infra-bony defects HA +DPBM	HA +DPBM approach in intrabony defects provides clinically relevant CAL gain and PPD reduction.
Sehdev et al 2016	RCT – Parellel group 6 months	24	Esterified HA fibers (Hyaloss)	Interproximal infra-bony defects HA + ResorbM, ResorbM (Bio-mesh)	Significant added benefit in CAL gain, PPD reduction defect fill
Santana et al 2015	RCT Split mouth – 12 months	60	rhFGF-2/ HA (Ossigel)	Intrabony defect OFD +rhFGF-2/ HA OFD	Significantly improved clinical parameters of periodontal wound healing one year after treatment
Briguglio et al 2013	RCT parallel group – 12 months	60	HA fibers (Hyaloss matrix)	Interproximal two-wall infra-bony defect OFD (Simplied papilla preservation flap)+EDTA +HA	Significantly improved clinical parameters,Probing depth reduction

				OFD+ HA	
Fawzy – El sayed et al 2012	RCT Split mouth -6 months	14	0.8 % Hyaluronan gel (Gengigel)	Interproximal intrabony defects OFD (MWF) + HA	Significantly improved clinical parameters,Probing depth reduction and gingival recession
Ballini et al 2009	Clinical report – 24 Months	9	Esterified HA with benzyl alcohol (HYAFF)	1 to 3-wall infra-bony defects HA +AutoG	HA +AutoG Have a good capacity in accelerating new bone formation in infrabony defects
Bogaerde et al. 2009	Clinical report – 12 Months	19	HA (Hyaloss®)	One/two-wall Infra-bony defects HA (Hyaloss®) + OFD	Clinical parameters like PPD, CAL improved but gingival recession increased.
Engstrom et al 2001	RCT – 12 MONTHS	15	14mg of hyaluronan (Syringe form)	Intrabony pockets (Surgical grou p (HA+GTR) /Non surgical group(HA + SRP)	In surgical group increased bone height IN SITES treated with HA +GTR.

Table 4: Systematic Reviews on Effect of HA in Alveolar Bone Regeneration.

AUTHOR	STUDIES INCLUDED	CONCLUSION
BI OSTOS -Aguilar et al 2023	276	**Objective:**Effects of hyaluronic acid (HA)alone or in combination with any bone substitute for the treatment of intrabony defects (IBDs). **Conclusion:**Compared with OFD alone, local application of HA in the treatment of IBDs provided a significant CAL gain and PD reduction at 6 months.
Salwa -A Aldahlawi et al 2023	725	**Objective**:clinical and radiological benefits of hyaluronic acid in periodontal infrabony defects. **Conclusion** :The meta analysis indicates that significant benefits of HA in terms of reduction in probing pocket depth , bone defect depth gain in clinical attachment level.
Manuel Rodriguez Aranda et al 2022	9	**Objective** :To evaluate the clinical and radiographic outcomes of hyaluronic acid (HA) application alone and in combination with other therapies for the surgical treatment of periodontal intrabony defects

		Conclusion :The application of HA can provide moderate and beneficial clinical and radiographic results for the surgical treatment ofperiodontal regeneration
Meizi – Elizier et al 2019	13	**Objective** :Benefit of topical application of HA On clinical outcomes following non-surgical and surgical periodontal therapy. **Conclusion** :The adjunctive use of HA may improve the clinical outcomes when used in conjunction with non-surgical and surgical periodontal therapy

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