

# Challenges of regeneration

GBR, Mucositis, Recession Coverage, Intrabony Defects,  
Furcation



# Tissue Regeneration common challenges

GBR

- Residual inert particles (instead of natural bone)
- Low density of new bone
- Inflammation

Mucositis

- Uncontrolled infection
- Plaque
- Risk of bone resorption

Recession

- Scare
- Healing time
- Infection

GBR

- Residual inert particles  
(instead of natural bone)
- Low density of new bone
- Inflammation

HA stimulates natural  
regeneration  
growth factors

Mucositis

- Uncontrolled  
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- Plaque
- Risk of bone  
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HA has a  
bacteriostatic effect

Recession

- Scare
- Healing time
- Infection

HA increase  
predictability

HA eases the  
inflammation

HA stimulates natural  
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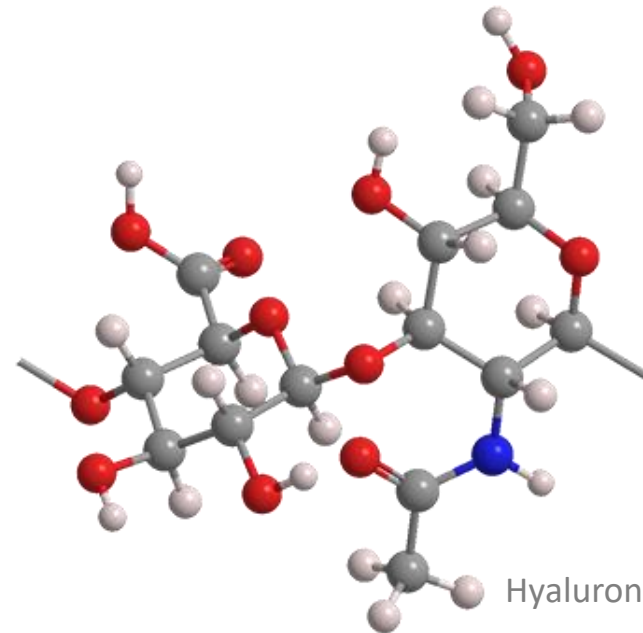
HA has a  
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inflammation

HA the key element of the human body<sup>1</sup>

- Extra cellular matrix is mainly composed of HA
- High molecular weight HA

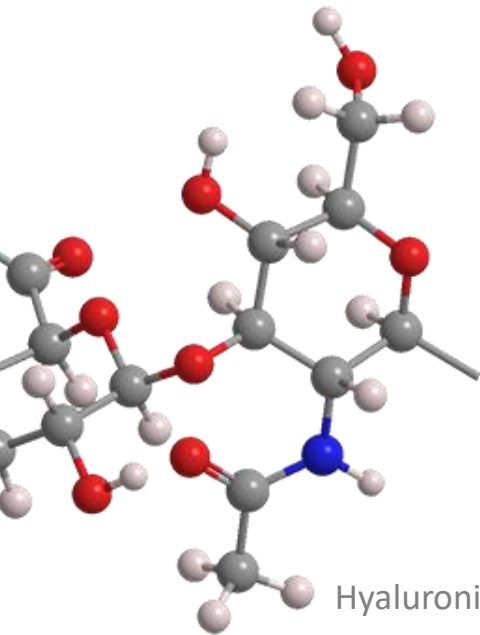


Hyaluronic Acid (HA)

Cross-linked hyaluronic acid gel

- Extended mode of action
- User friendly

1. Olczyk P. et al. 'Hyaluronan: structure, metabolism, functions, and role in wound healing.' Postepy Hig Med Dosw (Online) , 2008; 62:651–659 4 2)Salbach J et al. 'Regenerative potential of glycosaminoglycans for skin and bone' J Mol Med (2012) 90:625–635



## ACCELERATED TISSUE HEALING

Coordinates the post-operative inflammation process and accelerates neoangiogenesis (scarless) <sup>1,2</sup>

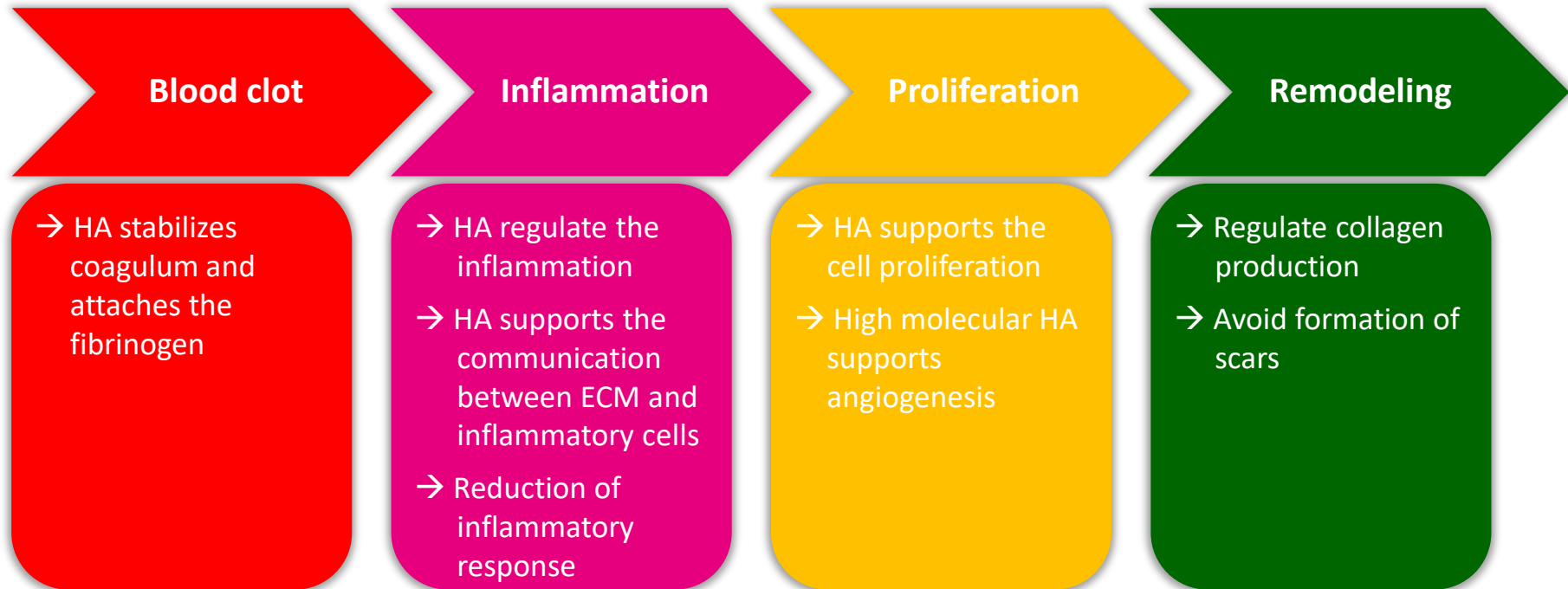
## SUPPORTS BONE REGENERATION

Stabilizes coagulum and support tissue regeneration <sup>1,2,3,4</sup>

## IMPROVED PREDICTABILITY

Bacteriostatic action and reduced pathogen penetration<sup>5</sup>

# The impact of hyaluronic acid



# HYADENT BG – the product

- Cross linked HA with high molecular weight
- Concentration: 1.8 %
  - 1.6% Cross linked HA
  - 0.2% natural HA
- Synthetic origin completely free of endotoxins
- Resorption time: 4-6 weeks
- Package: 2 cartridges, 1.2ml each



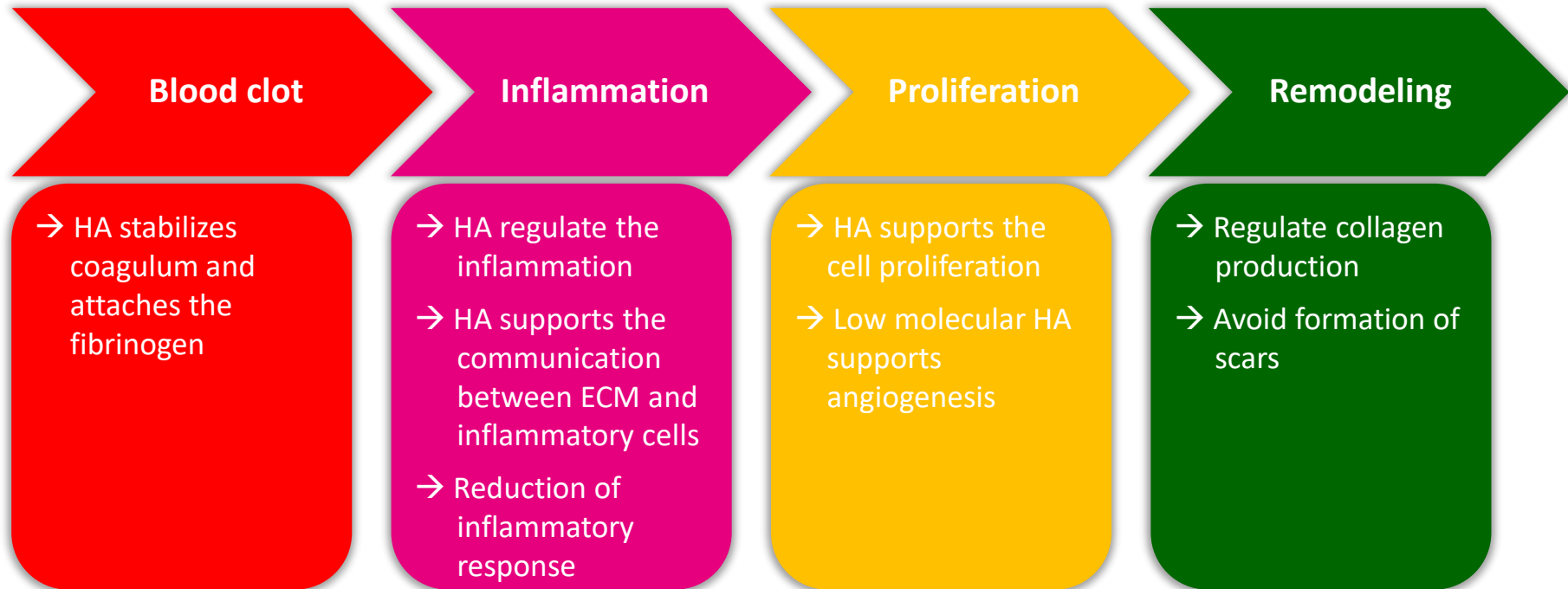
	Emdogain	PRF	Hyadent BG
Active ingredient	Enamel matrix protein (porcin tooth buds) + polypropylene alginate (PGA)	Patlet Rich Fibrin	Cross-linked hyaluronic acid at 1.8%
Volume / no. of patients	5 x 0,15 ml		2 x 1,2ml
Application	Open flap. Clean root surface + conditioning needed with EDTA (>2min) Site dry and free of blood → difficult technique / application dependent Flapless application → how apply on clean site and avoid inactivation with blood contact	GBR + Perio (recession mgt)	Open flap, flapless Apply gel on root, graft material (can be mixed with blood)  GBR + Perio (recession management) + Clean & Seal
Contraindication	uncontrolled diabetes, disease that compromise wound healing, steroid therapy, bone metabolic disease, radiation or other immuno-oppressive therapy and infections or vascular impairment at the surgical site.		Auto-immune disorders or under immunotherapy Active inflammatory or infection process. Coagulation defects or anticoagulant therapy Patient with hormonal disorders
Packaging, expiry	Cold storage, 24 mths		Room temperature, 24 months
Scientific documentation	Good documentation, first study in 1980s		Good documentation, molecule studies since 1934
Weakness	Meticulous application, inactivation in blood contact		
Price	EUR 470 for 5 units (EUR 94 for 0,15 ml)	EUR 3'000.- for equipment	EUR 150,00 (EUR 75 for 1,2ml)



# Scientific appendix



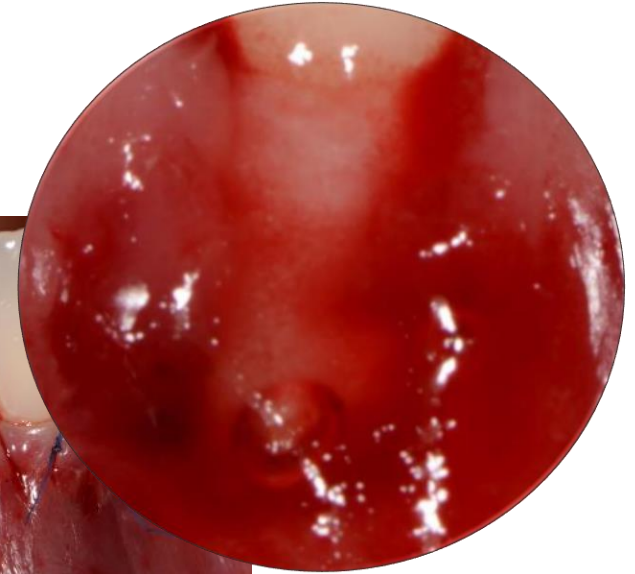
# The impact of hyaluronic acid



## Blood clot

Clinical case

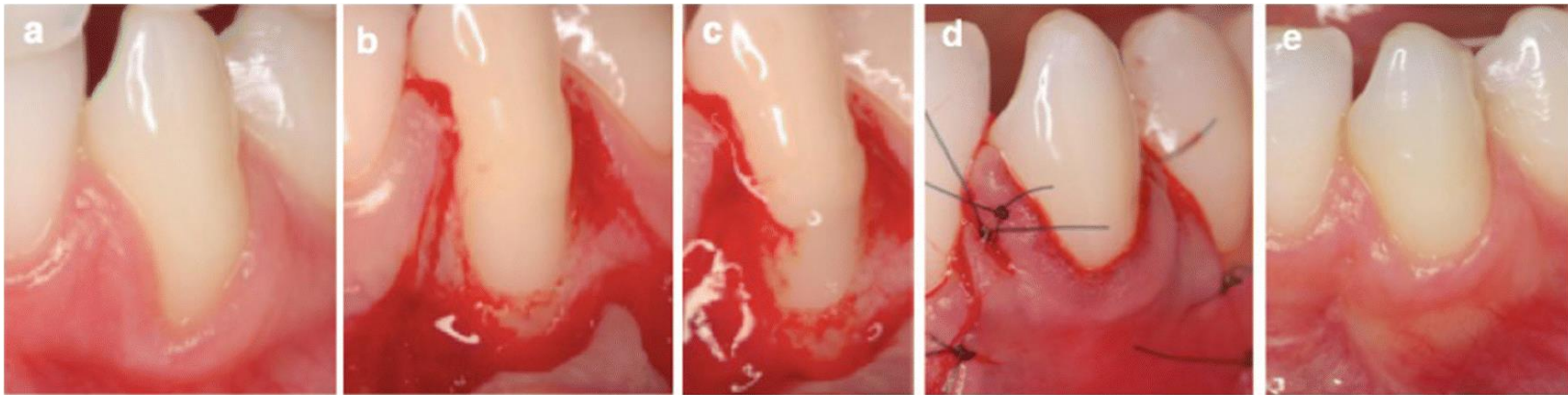
Gel stays on tooth surface due to viscosity and hydrophilicity.  
Both stabilize the blood clot to prompt the healing process.



## Inflammation

Randomized clinical  
trial

- HA represents an option to reduce patient morbidity by **reducing the swelling and discomfort**.
- Patient of the HYADENT BG Test group had **statistically significant less discomfort and swelling** vs Control Group

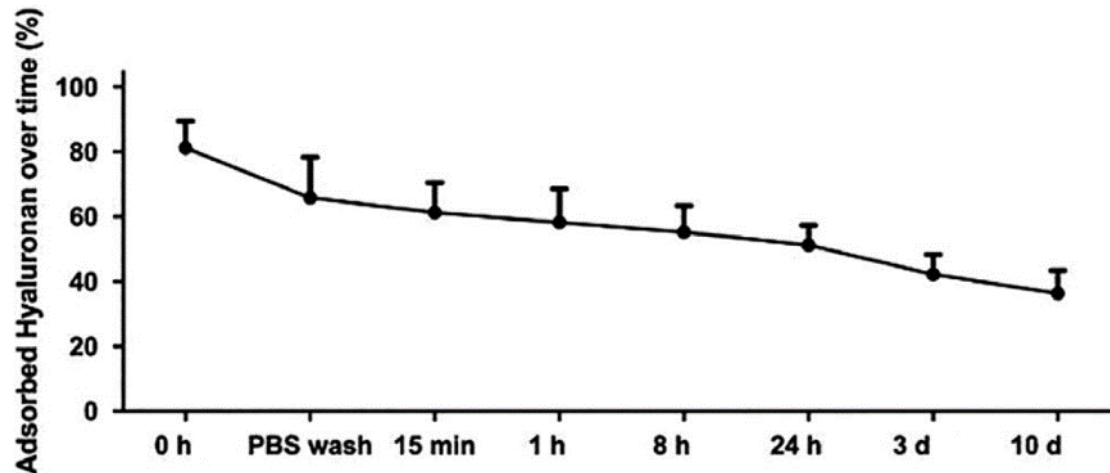


Parameters	Test	Control	<i>p</i> value
Pain intensity	0 [1]	1 [2]	0.151
Discomfort	1 [1]	2 [2]	0.029*
Swelling	1 [1]	2 [1]	0.010*

## Inflammation

In vivo studies

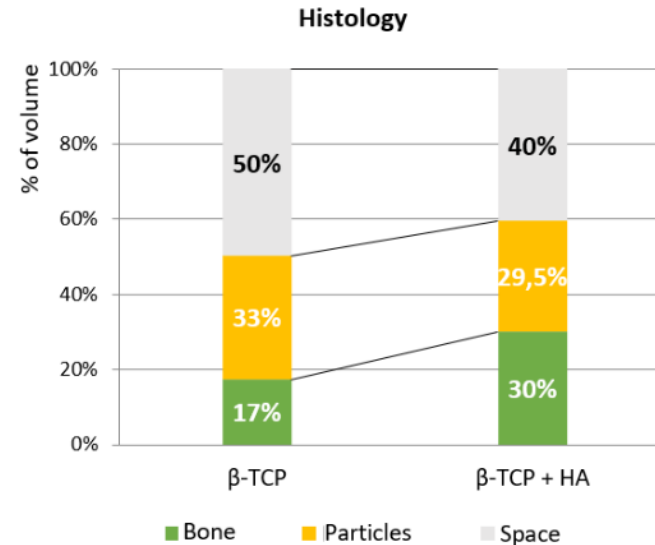
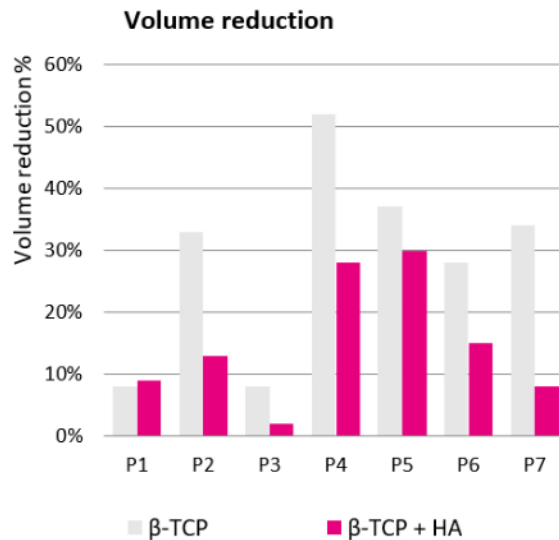
- Immersion of a collagen membrane (CM) in HA gel resulted in **delayed degradation**
- The “modulating” effect of HA on the chronic inflammatory processes encountered in uncontrolled diabetes, resulted in decreased levels of MMPs which in turn delayed collagen membrane degradation.
- 80% of the HA is adsorbed by the CM and **slowly released** into the surrounding medium



## Proliferation

In-vivo studies

Less bone graft volume reduction for HA group (statistically significant) for 6 out of 7 patients, compared to control group with bone chips only.



A statistically significant **higher amount of mature bone** (less space and residual particles of bone graft material) has been found within the HA group.<sup>1</sup>

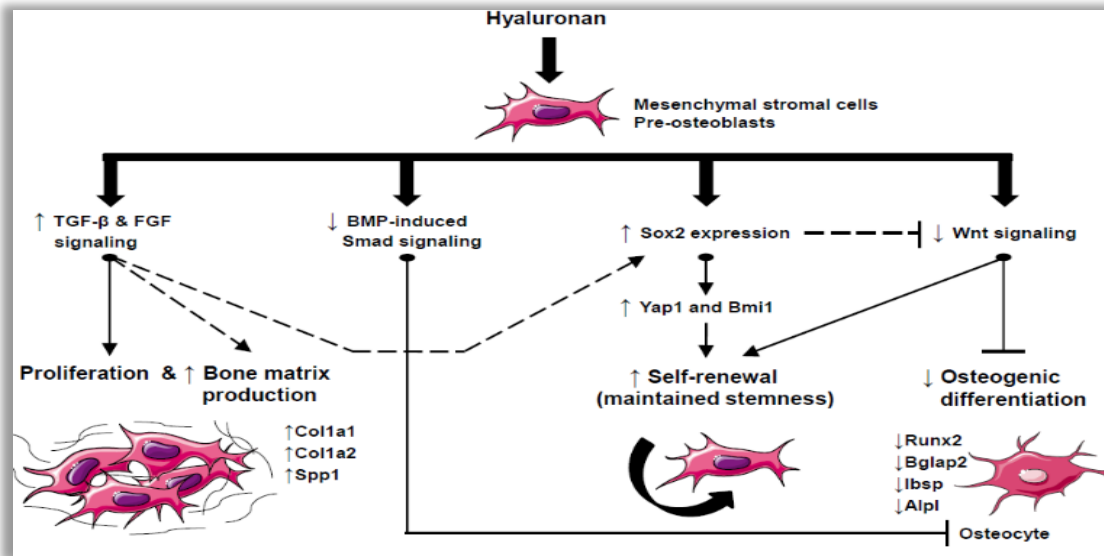
1. Stiller M. et al. 'Performance of  $\beta$ -tricalcium phosphate granules and pitty bone grafting materials after bilateral sinus floor augmentation in humans' Biomaterials 2014

## Proliferation

In-vitro studies

HA are biocompatible and enhance the proliferative, migratory and wound healing (scareless) properties of cell types involved in soft tissue wound healing following regenerative periodontal surgery.<sup>1</sup>

In gingival tissues, HA is not likely to impair the healing process by prolonging inflammation or causing excessive MMP expression at the repair site.<sup>1</sup>



HA preparations strongly induces the growth of osteoprogenitors and maintains their stemness, thus potentially regulating the balance between self-renewal and differentiation during bone regeneration following reconstructive periodontal and implant surgeries.<sup>2</sup>

1. Asparuhova M, Kiryak D, Eliezer M, Mihov D, Sculean A. 'Activity of two hyaluronan preparations on primary human oral fibroblasts'. J Periodontal Res 2018 Sep 27. Epub 2018 Sep 27 2. Asparuhova M, Chappuis V, Stähli A, Buser D, Sculean A, 'Role of two hyaluronan preparations in regulating self-renewal and osteogenic differentiation of mesenchymal stromal cells and pre-osteoblasts', 2020 (to be published)

## Proliferation

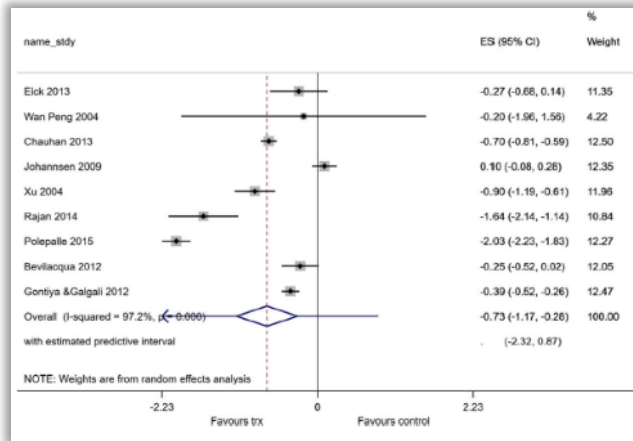
Systematic review

- The meta-analysis revealed that non-surgical treatment with adjunctive HA resulted in additional PD reduction (mean – 0.36 mm), CAL gain (mean 0.73 mm) and BOP reduction (mean – 15%) compared with conventional scaling and root planning after 3 months.<sup>1</sup>
- Both Hyadent (non-cross-linked) and Hyadent BG (cross-linked) maintained high PDL cell viability, increased proliferation, and early osteogenic differentiation.

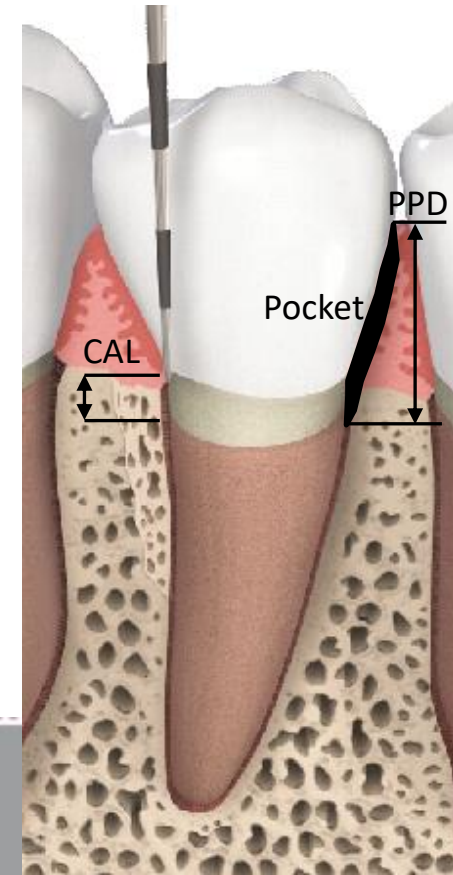
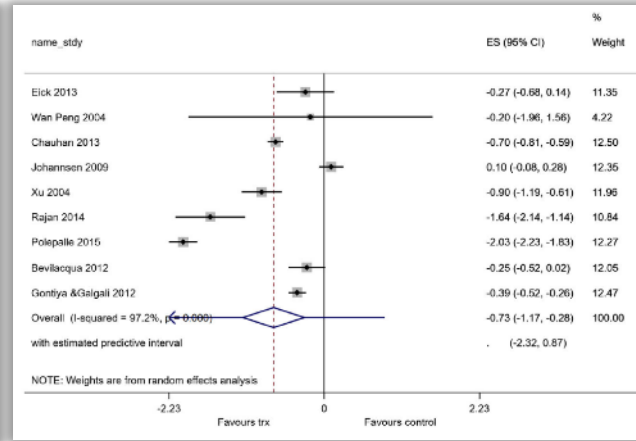


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### Clinical Attachment Level from CEJ



### Pocket Depth reduction



## Proliferation

### In-vivo studies

Effect of HA in mucogingival surgery in the coronally advanced flap (CAF) procedure in single Miller class I/recession type 1 (RT1) shows **higher recession reduction** with HA.

- Complete root coverage (CRC) of 80% for HA group vs 33% for the control group
- Clinical Attachment Level gain of 3.0mm for HA group vs 2.0 for the control group
- Recession reduction of 2.7mm for HA group vs 1.9mm for the Control group

Variables	CAF + HA baseline (n = 15); M [IQR]	CAF + HA 18 months (n = 15); M [IQR]	p value baseline versus 18 months <sup>a</sup>	CAF baseline (n = 15); M [IQR]	CAF 18 months (n = 15); M [IQR]	p value baseline CAF + HA versus CAF	p value baseline versus 18 months <sup>a</sup>	p value 18 months
Rec <sup>a</sup>	3.0 [1.0]	0.0 [0.0]	< 0.001*	3.0 [1.0]	1.0 [1.0]	0.216	0.001*	0.011*
RecRed <sup>a</sup>	–	2.7 [1.0]	–	–	1.9 [1.0]	–	–	0.007*
CAL <sup>a</sup>	4.0 [1.0]	1.0 [0.0]	< 0.001*	4.0 [1.0]	2.0 [0.0]	0.557	< 0.001*	0.011*
CAL-gain <sup>a</sup>	–	3.0 [1.0]	–	–	2.0 [1.0]	–	–	0.023*
PPD <sup>a</sup>	1.0 [0.0]	1.0 [1.0]	0.014*	1.0 [0.0]	2.0 [1.0]	0.087	0.008*	0.717
KT <sup>a</sup>	2.0 [1.0]	2.0 [0.0]	0.527	2.0 [1.0]	2.0 [1.0]	0.577	0.527	0.116
CRC <sup>b</sup>	–	80% (12/15)	–	–	33% (5/15)	–	–	0.025*
MRC <sup>c,d</sup>	–	93.8 ± 13.0%	–	–	73.1 ± 20.8%	–	–	0.003*

Performed statistical tests:

<sup>a</sup>Mann-Whitney U test

<sup>b</sup>Pearson's chi-square test

<sup>c</sup>Student's t test

<sup>d</sup>Data are expressed as mean and standard deviation; all other data are expressed as medians and interquartile range values

<sup>a</sup>Wilcoxon signed-rank test

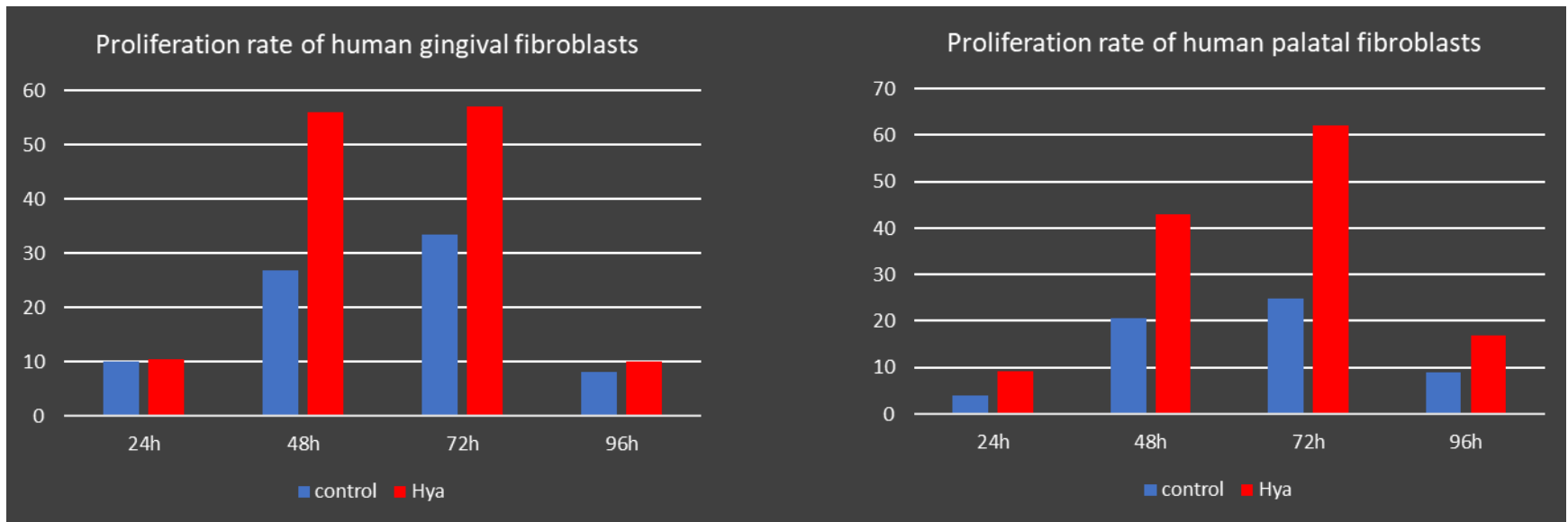
M median, IQR interquartile range, CAF coronally advanced flap, HA hyaluronic acid, M median value, IQR interquartile range, Rec recession depth, RecRed recession reduction, CAL clinical attachment level, CAL-gain clinical attachment level gain, PPD probing pocket depth, KT keratinized tissue, CRC complete root coverage, MRC mean root coverage

\*p < 0.05 indicates statistically significant differences

## Proliferation

### In-vitro studies

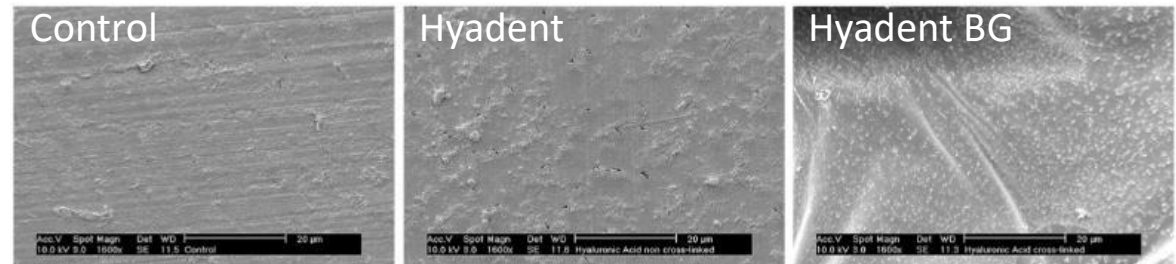
- Hyadent BG are extremely **biocompatible**<sup>1</sup> and support **scarless healing**<sup>2</sup>
- Hyadent BG increase the surface roughness essential for **cell adhesion and spreading onto dentin surfaces**.
- **Higher cell proliferation in the Hyadent BG** group in nearly all timepoints (24h, 48h, 72h and 96h) compared to the control group.<sup>2</sup>



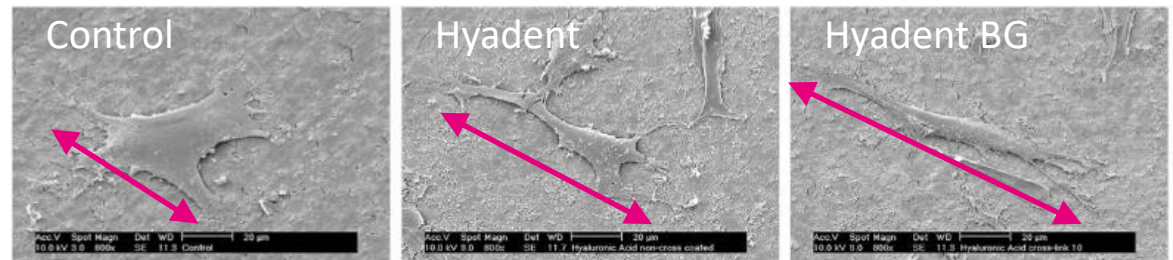
## Proliferation

In-vitro studies

- Hyadent BG are extremely biocompatible
- Hyadent BG increase the surface roughness essential for **cell adhesion and spreading onto dentin surfaces**. Both pre-requisites for the regeneration of periodontal tissues.<sup>1</sup>



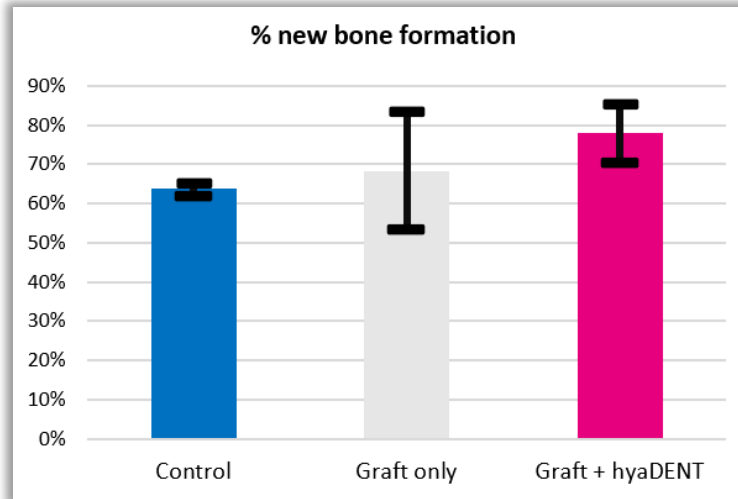
- Hyadent BG applied to dentin surfaces provide an optimal surface topography resulting in **advanced cell attachment**.<sup>1</sup>



1. Mueller A, Fujioka-Kobayashi M, Mueller HD, Lussi A, Sculean A, Schmidlin PR, Miron RJ. 'Effect of hyaluronic acid on morphological changes to dentin surfaces and subsequent effect on periodontal ligament cell survival, attachment, and spreading' Clinical Oral Investigations 2016 May .DOI 10.1007/s00784-016-1856-6

## Proliferation

Animal studies



After 8 weeks, a graft mixed with HA appears to be more efficient in osteoconduction for preservation of alveolar socket. Study on rabbits.<sup>1</sup>

- Control: only blood after tooth extraction(63.1%)
- Group 2: Group withgraft ( $\beta$ -TCP or hydroxyapatite ) only (68.3%)
- Group 3: graft + hyaDENT BG had the highest amount of bone (78.1%)

After 6 weeks, the HA group shows better ossification (rat tibial fracture)

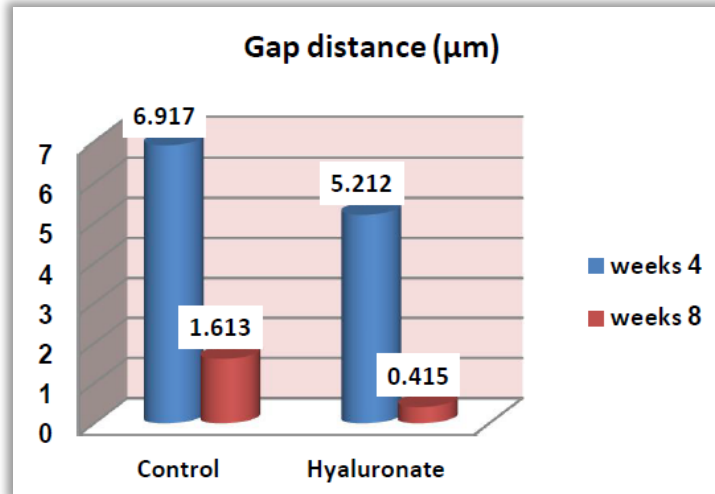
- HA group (88.8 +/- 13.3%).
- PRF group (50.7 +/- 28.2%)
- Control (76.3 +/- 21.7%)

Group	C Mean $\pm$ SD	HA Mean $\pm$ SD	PRF Mean $\pm$ SD	F*	P*
<i>Total ossification</i>					
2nd wk	26.1 $\pm$ 6.6	54.7 $\pm$ 9.7	75.3 $\pm$ 19.2	22.895	<0.001
6th wk	76.3 $\pm$ 21.7	88.8 $\pm$ 13.3	50.7 $\pm$ 28.2	6.210	0.008
T <sup>†</sup>	5.426	5.834	2.043		
P <sup>†</sup>	<0.01	<0.01	0.06		

C, control; HA, hyaluronic acid; PRF, platelet-rich fibrin; SD, standard deviation.  
 \*One-way analysis of variance.  
<sup>†</sup>Independent sample t-test. <sup>‡</sup>P < 0.05.

## Proliferation

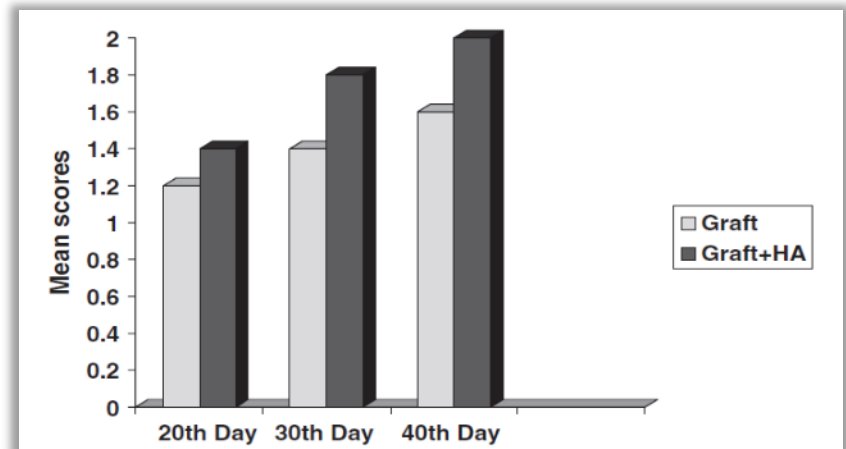
Animal studies



Coating the implant surface with **hyaluronate significantly improves bone to implant** contact and osseointegration.<sup>1</sup> After 8 weeks the gap between the bone and

- The implant is 1,61  $\mu\text{m}$
- The implant with HA is only 0,415  $\mu\text{m}$

- The cavities that have been filled with **HA and bone graft** have shown **higher scores every period** of the study compared to the control group during.
- HA is one of the essential components of extracellular matrix which plays a predominant role in tissue morphogenesis, cell migration, differentiation, and adhesion.

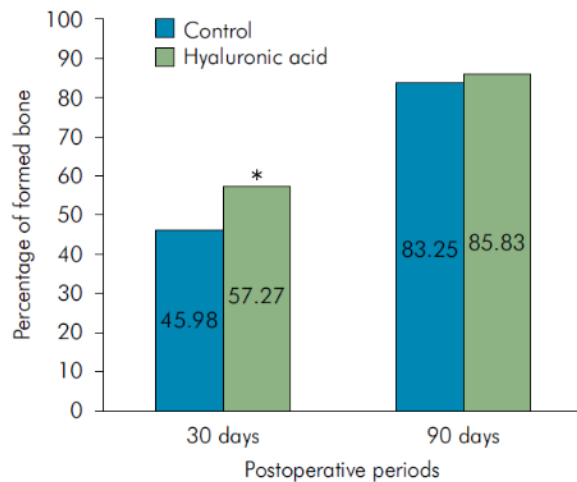


1. Ghada Bassiouny A. 'Bioinspired Approach for Dental Implant Functionalization: An Experimental Study Evaluating the Effect of Hyaluronate as Bioactive Implant Coating.' J Am Sci 2013;9(11):187-192]. (ISSN: 1545-1003). <http://www.jofamericanscience.org>. 25 2. Muzaffer A. et al. 'The Effect of Hyaluronic Acid-supplemented Bone Graft in Bone Healing: Experimental Study in Rabbits' J Biomater Appl 2006 20:209

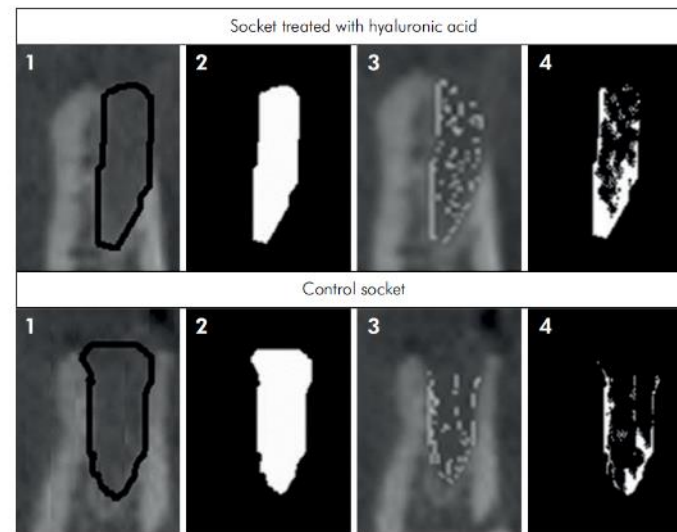
## Remodeling

In-vivo study

- The experimental model adopted (split-mouth) where each patient got one extraction socket filled with blood clot (Control) and HA (Test Group).
- At 30 days, it was observed that **bone formation was more advanced in sockets filled with HA.**



**Figure 4.** Percentage of newly formed bone in tooth sockets of hyaluronic acid (HA) and control groups at 30 and 90 days after surgery. \* $p < 0.05$  (Paired t test).



**Figure 3.** Representative slices of cone beam computed tomography of control and 1% hyaluronic acid (HA)-treated sockets at 30 days after tooth extraction. Top panel - socket treated with HA; bottom panel - control socket. 1 - delimitation of the region of interest (dental socket); 2 - total area of the socket; 3 - overlapped area of intra-alveolar newly formed bone; 4 - demarcation of high intensity areas.

