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REVIEW ARTICLE

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Hyaluronic acid injection to restore the lost interproximal papilla: a systematic review

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ABSTRACT

Objectives: To assess the efficacy and safety of hyaluronic acid (HA) injections to restore the lost interproximal papilla.

Materials and Methods: A systematic literature search was conducted in PubMed/MEDLINE, Scopus and Cochrane electronic databases with no time restriction up to September 2021. Any clinical study evaluating HA injection into the interproximal papilla loss Class I and II according to Norland & Tarnow, were included based on the following PICO questions (1) Are HA injections effective for the reconstruction of the interproximal papilla loss? (2) What are the side/adverse effects of using HA for the reconstruction of interproximal papilla loss? The risk of bias assessment was performed using the Cochrane Collaboration's the Newcastle Ottawa and Joanna Briggs institute tools.

Results: A total of 1497 titles were retrieved. From these, eleven were included and underwent full data extraction. However, due to heterogeneity in the data among the included articles, a meta-analysis could not be performed. Three articles reported no-differences in term of papilla tip to contact point distance or the papilla fill reduction. Finally, five studies showed a reduction in the black triangle with a percentage range between 19 and 47%.

Conclusion: The non-surgical use of HA injection seems to have a positive effect on the re-establishment of interproximal papilla lost. However post-operative complications might develop.

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KEYWORDS
Hyaluronic acid; interdental papilla; non-surgical approach; papilla reconstruction

Introduction

The gingival tissue area located between the interproximal alveolar bone (IAB) and the contact point (CP) constitutes the interproximal papilla. The papilla loss might lead to 'black triangles' (BTs), which are mainly related to the periodontal attachment loss, but also to inadequate contours of restorations or prosthetic crowns [1], diastemas [2], abnormal tooth shape, an increased distance between CP and alveolar bone as well as to traumatic interproximal hygiene habits [3], gingival biotype and periodontal disease [4,5]. The development of BTs produces aesthetic and phonetic problems, especially if located in the aesthetic zone [6,7]. Therefore, several non-surgical and surgical procedures have been proposed to re-create the lost interproximal tissue. More specifically, micro-surgical mucogingival procedures have been tested [8–10], but their efficacy is limited and the treatment outcomes remain unpredictable due to the limited vascular supply of the papilla which does not allow an optimal healing [11]. Non-surgical techniques revolve around correction of the habits, prosthetic and spatial factors [1–3,12]. However, the non – surgical techniques are more time consuming and less-invasive [1]. To obtain faster short results, the infiltration of different growth factors (i.e. platelet-rich plasma [13], fibroblasts [14], stem cells [15], hyaluronic-acid (HA) has been implied with promising short-term results. HA is an essential glycosaminoglycan of high density associated to collagen molecules or proteoglycans, contributing the extracellular matrix to be more resistant providing regenerative and restorative properties to the tissue

However, there are still some concerns on its routinely clinical use due to the lack of clinical outcomes predictability [16,17] and due to the onset of post-operative adverse effects such as swelling and extreme tenderness with a burning sensation on the lip [18]. To the authors' best knowledge, no systematic review has been performed to summarise the current evidence on the use of HA locally injected for the reconstruction of missing papillae. Therefore, the aim of the present study was to assess the efficacy and

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safety of HA injections in patients with interproximal papillae loss.

Method and materials

The present systematic review was conducted following the PRISMA guidelines [19], the following focussed PICO (population, intervention, comparison, and outcome) questions were developed:

1. Are HA injections effective for the reconstruction of the interproximal papilla loss?
2. What are the side/adverse effects of using HA for the reconstruction of interproximal papilla loss?

The following inclusion criteria were applied: any human clinical study (i.e. RCTs, cohort studies or case series) published in English, Italian and Spanish. No restriction with respect to the first follow-up examination were applied.

The population (P) of the selected studies should include individuals with interproximal papillary loss who received HA injections as intervention (I) to restore the interproximal papillary loss, which may be compared (C) to a control group (i.e. placebo and/or other material, if available). The investigated outcomes (O) were: (1) vertical papilla gain in millimetres (mm), (2) volume change of interdental papilla (mm^2), (3) or the reduction of the BT (%).

The vertical papilla gain (mm) could be evaluated as the distance between papilla tip and contact point (PT-CP) or the distance between papilla tip and the apical margin of the stent cast. All related studies included might analyse the results with digital analysis program or morphometric measurements. Regarding gingival volume changes (mm^2) and/or reduction of the BT (%), the results could be evaluated using morphometric measurements with a periodontal probe calibration and compared with pixels and image analysis programs.

The exclusion criteria were, (1) studies that did not assess the use of HA for papillary reconstruction in patients with interdental papillary loss; (2) studies that evaluated the use of HA in conjunction with graft tissue surgery; (3) review articles; (4) case reports; (5) commentaries; (6) letters to the editor, or (7) unpublished articles.

Information sources

A comprehensive search of the literature was conducted with the no time restriction up to September 2021 in the following electronic databases: PubMed/MEDLINE, The Cochrane Library and Scopus. The search strategy was realised using the following combination of free text and keywords and MeSH terms adapted to each database: ((hyaluronic acid) OR (HA) OR (hyaluronic acid filler) OR (ha filler injection) OR (injectable hyaluronic acid gel) OR (hyaluronic acid gel injection) OR (hyaluronan) OR (HY) OR (hyaluronan injection) OR (local injection) OR (filler) OR (filler injection) OR (dermal filler) OR (biodegradable filler) OR (glycosaminoglycan)) AND ((papilla) OR (papillae) OR (papilla defect) OR (interdental papilla) OR (interdental papillae) OR (pyramidal papilla) OR (interproximal papilla) OR (gingival papilla) OR (gingival interdental papilla) OR (gingival interdental papilla defect) OR (papilla reconstruction) OR (missing papilla) OR (black triangle) OR (black triangle space) OR (gingival black triangle) OR (contact point) OR (embrasure) OR (embrasure morphology) OR (papillary recession) OR (papillary deficiency) OR (recession) OR (papilla reconstruction) OR (papilla loss) OR (gingival papilla loss) OR (papilla volume augmentation) OR (deficient papilla) OR (interdental papillary deficiency) OR (papilla augmentation) OR (interdental papilla augmentation)).

Two independent researchers (ACC and AR) compared search results to ensure completeness and duplicated papers were removed. Full titles and abstracts of the remaining papers were screened individually. Finally, full text articles were selected according to the criteria described above. Differences in eligible studies were resolved by discussion with a third reviewer (JGS). Cohen's kappa score was calculated to measure the interrater agreement (Interrater agreement: 82.5%; Cohen's kappa score of 0.712: substantial agreement). The references of the included studies were also reviewed for possible inclusion.

Two independent reviewers (ACC and AR) extracted the data. Any disagreements were solved by discussion with a third reviewer (JGS). Data extraction included the following information: The general characteristics of the selected papers: first authors, type of study, recruitment of patients, sample characteristics (population, age, and gender), number, location and type of papilla analysed, inclusion and exclusion criteria and clinician that performed the injections (Tables 1 and 2); Description of the methods used in the selected studies: author and year of publication, type of hyaluronic acid, number of injections, number of sessions, injection technique, post-surgical medication, measurements tools, patient satisfaction and complications (Table 3); Papilla volume changes: vertical gain (mm), gingival volume change (mm^2) and reduction of BT area (%) (Table 4).

Risk of bias in individual studies

Two independent reviewers (ACC and AR) assessed the methodological quality of the included studies, and any disagreement was resolved with the assistance of a third researcher (JGS). The Joanna Briggs Institute (JBI) standardised critical appraisal instrument was used for case series studies, which incorporates 10 questions [20]. Based on the answers, an overall of 5 or less 'Yes' were considered as the study would have a high risk of bias, while more than 5 'Yes' would consider the study to have a low risk of bias. Controlled clinical trials were evaluated following the Cochrane Collaboration's tool for assessing risk of bias, which incorporates 7 domains [21]. The studies were classified as low risk of bias (low risk of bias for all key domains], unclear risk of bias (unclear risk of bias for 1 or more key domains) and high risk of bias (high risk of bias for 1 or more key domains) [21]. In addition, the quality of prospective studies was assessed with the modified Newcastle Ottawa scale [22].

Table 1. General characteristics of the selected studies.

Author, year (City, Country)	Type of study	Sample	Age (years)	Gender	Papillae analysed (Mx/Mb)	Classiffication and type of papilla	Inclusion criteria	Exclusion criteria	Periodontal treatment	Number of operators
Becker et al., 2010 (Tucson, USA)	Case series	11 cases	55.8	4M/7 F	14 14 Mx/0 Mb	–	Deficient papillae adjacent to teeth or implants	–	–	–
Mansouri et al., 2013 (Teheran, Iran)	Case series	11 cases	37.5 ± 14.4	3 M/8 F	21 21 Mx/0 Mb	Maynar Miller 18 type I and 3 type III	Age range of 20–75 years, Plaque index *of* < 20%, No caries, no fixed prosthesis or orthodontic appliance, Non-smoker, No history of systemic disease affecting the periodontal status, No consumption of drugs causing gingival hyperplasia	–	Supragingival debridement in cases of bad plaque control	–
Awartani et al., 2016 (Riad, Saudi Arabia)	Case series	9 cases	36.4	0M/9 F	17 13 Mx/4 Mb	Nordland y Tarnow 13 class I and 4 class II	Adults (≥18 years old), systemically healthy, at least one maxillary or mandibular anterior interdental space exhibiting class I or II interdental papilla loss	Non history of allergic reaction to injectable filler; Non-smoking, pregnancy and lactation; No medications affecting the gingiva or wound healing; No periodontal surgery in the last 12 months; No carious lesions or fixed restorations on study teeth, periodontitis; Non plaque control (visible plaque present, full mouth plaque score > 20 %)	Oral hygiene + Supragingival debridement in cases of bad plaque control	–
Bertl et al., 2016 (Vienna, Austria)	RCT	11 cases 10 controls	30 ± 6.4	6 M/5 F cases 3M/7 F controls	21 (11 cases and 10 controls) 21 Mx/0 Mb	Modified papilla index score MPIS 21 score 0	≥ 18 years of age, implant restoration finalised >6 months ago, at least one deficient papilla in the anterior maxilla (first premolar to first premolar) between a natural tooth and an implant-supported crown.	No contact point, Inadequate plaque control (full-mouth plaque score > 20%), Probing depth > 5 mm, or buccal gingival recession > 3 mm, or < 2 mm keratinised tissue at the adjacent tooth/ implant, Systemic disorders (e.g. uncontrolled diabetes, malignancy) or regular intake of medications affecting connective tissue metabolism	–	The same surgeon
Lee et al., 2016 (Gwangju, Korea)	Case series	13 cases	32	6M/7 F	57 57 Mx/0 Mb	–	At least 1 papillary deficient site in the upper anterior area. plaque index and gingival index must be between 0 and 1	Pregnant, Patients taking medication that increase the risk of gingival enlargement, Orthodontic treatment on the upper anterior area	–	–

(*continued*)

Table 1. Continued.

Author, year (City, Country)	Type of study	Sample	Age (years)	Gender	Papillae analysed (Mx/Mb)	Classiffication and type of papilla	Inclusion criteria	Exclusion criteria	Periodontal treatment	Number of operators
Abdelraouf et al., 2019 (Cairo, Egypt)	RCT	4 cases 4 controls	32.55 ± 9.3	–	30 (16 cases and 14 controls) -	–	At least one deficient papilla in the inter-bicuspid region, Papillary deficiency types I or II, according to Nordland and Tarnow classification, Distance between the contact point and inter-proximal bone crest of ≤ 7 mm and probing depth of ≤ 4 mm at the deficient papillary sites, Full mouth plaque index and gingival index scores should be between 0–1, No open contacts between affected teeth, Teeth free from caries, proximal restorations, fixed prosthesis or orthodontic appliances	Subjects with medical conditions that may affect periodontal healing or regeneration, Subjects with a history of allergic reactions, pregnant or breastfeeding females, smokers and alcoholics, Patients with current or previous drugs intake that may predispose to gingival enlargement, Patients under orthodontic treatment or had orthodontic treatment in the past six months, Patients with a history of traumatic oral hygiene measures or periodontal surgeries over the last six months at the area of interest	Supragingival and subgingival debridement + oral hygiene techniques	The same surgeon
Ni J et al., 2019 (Shanghai, China)	Case series	8 cases	41.6	0M/8 F	22 17 Mx/5 Mb	Nordland y Tarnow 11 class I and 11 class II	Adults (20–60 years old), No systemic disease, Good oral hygiene (full mouth plaque score < 20%), At least one interdental papilla loss (Class I or Class II) in the anterior maxilla or mandible, Healthy periodontal tissue or the inflammation is controlled.	Fixed prosthesis or carries on the study teeth, No contact point on the study teeth, History of allergic reaction to injectable filler, Periodontal surgery in the last 6 months, Regular medication intake affecting the gingiva metabolism	Supragingival scaling in cases of inflammation	The same surgeon
Singh et al., 2019 (Karnataka, India)	Prospective cohort	8 cases	29.6–30.6	2M/6 F	35 17 Mx/18 Mb	–	Clinically normal periodontium other than deficient papilla with Cardaropoli Papilla Presence Index score 2 and 3 and with full mouth plaque score < 10%	Allergy to hyaluronic acid, poor plaque control, medically compromised, teeth with hopeless prognosis, parafunctional habits, traumatic occlusion, patient who had undergone periodontal plastic surgery for the selected area in the last 1 year, adjacent teeth with caries, fixed prosthesis, or orthodontic appliance, drug-induced gingival overgrowth, pregnant and lactating woman, and smokers	–	–

(*continued*)

Table 1. Continued.

Author, year (City, Country)	Type of study	Sample	Age (years)	Gender	Papillae analysed (Mx/Mb)	Classiffication and type of papilla	Inclusion criteria	Exclusion criteria	Periodontal treatment	Number of operators
Spano et al., 2019 (Toronto, Canada)	Case series	3 cases	51.7 ± 12.7	0 M/3 F	4 4 Mx/0 Mb	Nordland y Tarnow 2 class I, 1 class II and 1 class III	Patients who presented were dissatisfied with their papillary aesthetic	Individuals with clinical signs of active periodontitis or gingivitis	Scaling of the interdental space and adjacent teeth was performed with hand curettes	–
Turgut et al., 2020 (Gazi, Turkey)	Prospective cohort	20 cases	34	10M/10 F	200-	–	Presence of open interdental embrasure in their natural teeth, No systemic disease were non-smokers, and not pregnant or lactating, No diagnosis of periodontitis, and no use of antibiotics or any drugs that may affect the periodontal tissues in the last 3 months, Without any prosthetic restoration in the maxillary and mandibular anterior regions, Having five interdental papillary spaces in the inter canine–canine region	No contact point, insufficient plaque control, pocket depth *of* > 3 mm in the treated areas, an*d* < 2 mm keratinised gingiva.	Supragingival and subgingival debridement + oral hygiene techniques	The same surgeon
Alhabashneh*et al.*, 2020 (Irbid, Jordan)	Prospective cohort	21 cases	36.9 ± 9.6	7 M/14 F	86 58 Mx/28 Mb	Nordland y Tarnow 57 class I and 29 class II	Caucasian non-smoking patients aged above 18 years Had at least one site with interdental papilla recession in the anterior region (central incisors, lateral incisors and canines) of the maxillary or mandibular jaws. Papillary deficiency types I or II, according to Nordland and Tarnow classification. The distance from the contact point to alveolar bone cres*t* ≥ 5 mm. No active periodontal diseases and good oral hygiene.	Spacing or crowding between the teeth to be treated, abnormal tooth shape, sys- temic diseases such as diabetes mellitus, hypertension or conditions that alter the outcome of periodontal therapy. Pregnant and lactating women and tobacco users.	Supragingival and subgingival debridement + oral hygiene techniques	–

M: Male F: Female Mx: Maxilla. Mb. Mandible.

Table 2. Characteristics of the provided interventions in the selected studies.

Author, year (City, Country)	Intervention (Test)	Intervention (Control)
Becker et al., **2010** (Tucson, USA)	Local anaesthetic was administered. Hyaluronic-based gel (less than 0.2 mL) was injected 2–3 mm apical to the tip of the papilla	–
Mansouri et al., **2013** (Teheran, Iran)	Local anaesthesia administration and less than 0.2 ml hyaluronic acid gel was injected at the base of the papilla. The procedure was repeated 3 weeks and 3 months	–
Awartani et al., **2016** (Riad, Saudi Arabia)	Local anaesthesia and 0.2 ml of the cross-linked hyaluronic acid clear gel: 1 was injected directly into the middle of the papilla, 2– 3 mm apical to the tip of the papilla. Injection was followed by gentle massage of the area for 1 min. Treatment was repeated at 21 and 42 days	–
Bertl et al., **2016** (Vienna, Austria)	Local anaesthesia gel and injection of 1 ml of the gel contains 16 mg cross-linked Na-hyaluronate and 2 mg Na-hyaluronate. Delivery was performed using pressure syringe for standardised dose delivery (0.06 ml per "click") and a 3-step technique. Treatment was repeated at 28 days	Same as Test group but with the delivery of saline solution
Lee et al., **2016** (Gwangju, Korea)	The single application volume of the injection-assisting device was set to 0.002 cc. The injectable hyaluronic acid gel was applied 2 to 3 mm below the interdental papilla tip. Treatment was repeated up to five times during 3-weeks	–
Abdelraouf et al., **2019** (Cairo, Egypt)	Local anaesthesia administration and infiltration of 0.1 mm of hyaluronic acid gel using a 30-gauge disposable insulin syringe. The needle was inserted 2–3 mm apical to the papilla tip	Same as Test group but with the delivery of saline solution
Ni J et al., **2019** (Shanghai, China)	Local infiltration anaesthesia and an injection of the hyaluronic acid gel at the base of the deficient papilla. Two additional injections were performed 3 weeks and 6 weeks	–
Singh et al., **2019** (Karnataka, India)	Local infiltration anaesthesia and an injection < 0.2 ml of the hyaluronic acid gel 2–3 mm apical to the coronal tip of the papilla. Injection was repeated on 2nd and 3rd weeks	–
Spano et al., **2019** (Toronto, Canada)	Local anaesthetic and a 3 to 5 mm horizontal incision was made in the alveolar mucosa 2 mm apical to the mucogingival junction. Subsequently, additional dermal filler was administered for a total of 0.2 to 0.6 mL per papilla. No sutures	–
Turgut et al., **2020** (Gazi, Turkey)	Local anaesthetic and application of with hyaluronic acid filler injection to consecutive papillae regions	–
Alhabashneh*et al.*, **2020** (Irbid, Jordan)	Local anaesthesia delivered and hyaluronic acid gel injected in a three-step technique. Injections were repeated 21 days after the first injections.	–

Results

Selection of studies

The search strategy yielded 1437 articles, of which 736 remained after removing the duplicates. Thereafter, 2 independent researchers (ACC and AR) reviewed all of the titles and abstracts and excluded 538 titles that did not address the issue, obtaining 20 potential references. Thereafter, 9 articles were discarded with reasons: two were literature reviews, two were case reports, one had the same study with same authors in different journal one did not evaluate vertical and surface gain of the papilla effect of the HA, and three studies evaluated the effect of HA with a gingival graft surgery. Finally, 11 papers were included and underwent full data extraction [23–33] (Figure 1). Interrater agreement was 82.5% with a Cohen's kappa score of 0.712 (substantial agreement).

Characteristics of included studies

From the 10 articles, six were case series [23–25,27,29,31], two randomised clinical trials [25,27] and three prospective studies [30,32,33]. The selected articles were published between 2010 and 2020. A total of 133 patients (507 sites), 184 were cases (483 sites) and 14 were controls (24 sites). All analysed papillae were in the anterior aesthetic location [23–33]. Regarding gender, there were 84 females and 41 males. Individuals age ranged from 29 to 60 years. None of the included patients had systemic diseases or were smokers [24–33] and only one study did not specify their inclusion criteria [23]. For the initial treatment phase or bad plaque control, 5 studies performed oral hygiene techniques, supragingival debridement treatment plan [24,25,28,29,32], subgingival scaling treatment [28,32,33] or scaling of the interdental space and adjacent teeth with hand curettes [31]. Four studies did not specify any plaque debridement [23,26,27,30], four studies described that the injection was performed from the same clinician [26,28,29,32], whereas the remaining of studies did not specify [23–25,27,30,31,33]. Details of patients' characteristics and of the provided interventions are summarised in Tables 1 and 2.

Risk of bias assessment

Cases series

One study was assessed as low quality [27] and five studies were assessed [23,24,26,28,30] as high-quality according *Joanna Briggs Institute (JBI)* standardised critical appraisal instrument (Table 5). Among the limitations of these studies, we found that 5 of them did not specify the period of time in which the patients were treated or whether they were consecutive patients [23–25,27,29]. Moreover, one study did not specify inclusion/exclusion criteria [23], 3 studies used a classification of Nordland y Tarnow for the papilla defects [25,29,31], and 2 of them did not perform any type of statistical analysis [23,29].

Table 3. Description of the methods used in the selected studies.

Author, year	Anaesthetic	Type of HA	Injections per session	Number of sessions	Injection technique	Post-surgical recommendations	Papilla measurement tool	Patient Satisfaction	Complications
Becker et al., 2010	Septocaine	<0.2 ml of the HA gel	1	2–3 times (mean 2.43) 3 weeks intervals	2–3 mm apical to the tip of the papilla.	–	Photographs and pixel software analysis	–	–
Mansouri et al., 2013	–	<0.2 ml of the HA gel	1	3 times maximum 3 weeks intervals	2–3 mm apical to the coronal tip of the papilla.	Not to brush their teeth at the day of injection Oral hygiene the day after using a soft toothbrush. No interdental floss	Photographs and, pixel software analysis and periapical radiographs	–	–
Awartani et al., 2016	–	<0.2 ml of the HA gel	1	3 times 3 weeks intervals.	2– 3 mm apical to the tip of the papilla	24-h abstinence from mechanical plaque control	Photographs, study cast and picture software analysis	–	Pain/discomfort
Bertl et al., 2016	Xylocain 2%	*Hyadent Barrier Gel*	3	2 times 4 weeks after	Reation of a reservoir 2–3 mm apically to the tip of the deficient papilla. Below the base of the deficient papilla	–	Photographs, periapical radiographs, intraoral scans and Image analysis program	VAS = 30	Severe pain swelling. Painless granuloma
Lee et al., 2016	–	Teosyal Puresense Global Action®, Teoxane, Geneva, Switzerland 0.2 ml of the HA gel	1	5 times 3 weeks intervals	45° angle, 2–3 mm apical to the involved papilla	–	Photographs, periapical radiographs, pixel software and picture software analysis	–	–
Abdelraouf et al., 2019	Lidocaine 0.3%	(Restylane-Lidocaine cross-linked Hyaluronic Acid Filler, Galderma S.A, Sweden)	1	3 times 3 weeks intervals	45° angle, 2–3 mm tip to the involved papilla	Abstinence from mechanical plaque control in the area, the use of mouthwash twice daily	Photographs, periapical radiographs, picture software analysis, study cast	VAS = 45 ± 12.6	–
Ni J et al., 2019	4% articaine 1/100000 adrenaline	(Qi sheng biological agent company Limited, Shanghai, China)	1	3 times 3 weeks intervals	Base of the deficient papilla	–	Photographs and morphometric analysis of images	–	Bleeding
Singh et al., 2019	lidnocaine 2% 1/80000 adrenaline	<0.2 ml of the HA gel	1	3 times Baseline 2° and 3° week.	2–3 mm apical to the coronal tip of the papilla	–	Photographs, stent measurements and morphometric analysis of images.	–	Severe pain, itching, redness, ulcers to the local area or at lip, granulomatous lesion, swelling, abnormal patch, tenderness, bruising to the local site
Spano et al., 2019	Local anaesthetic	Juvéderm, Allergan, Markham, Ontario, Canada.	1	1 time	Deficient papilla and subperiosteal tissue space	0.12% chlorhexidine mouth rinse + ibuprofen.	Photographs and morphometric analysis of images	VAS = 62.46%	–
Turgut et al., 2020	Local anaesthetic	(hyaDENT BG, BioScience)	3	3 times 3 weeks intervals	Imaginary triangle	Control plaque + interdental tooth cleaning at 2° session	Photographs, intraoral scans and image analysis program	–	–
Alhabashneh et al., 2020	Local anaesthetic	(hyaDENT BG, BioScience)	3	2 times 3 weeks intervals	Base of the deficient papilla	Oral hygiene the day after Using a soft toothbrush use of mouthwash twice daily	Photographs and morphometric analysis of images	VAS =30	Mild pain

ml: mililiters. HA: Hyaluronic Acid. VAS: Visual Analogue Scale.

Table 4. Reported papilla volume gain within the included studies.

Controlled Trials													
Author	Follow up	Vertical papilla gain (mm)				Gingival volume change (mm2)				BT area (%)			
Year	(months)	Test	P value	Control	*p* Value	Test	*p* Value	Control	*p* Value	Test	Control	*p* Value	
Bertl et al., **2016***	BL	2.0 ± 1.1		2.3 ± 1.2		0.51 ± 0.31		0.51 ± 0.25		–	–		
	3	1.8 ± 0.7		2.2 ± 1.2		0.47 ± 0.20		0.49 ± 0.23					
	6	1.9 ± 0.8		2.2 ± 1.2		0.52 ± 0.26		0.54 ± 0.27					
	BL-3	−0.23 ± 0.68	0.296	−0.10 ± 0.39	.443	−0.04 ± 0.15.	.413	0.02 ± 0.07	.424				
	BL-6	−0.09 ± 0.63!	0.640	−0.15 ± 0.41	.279	0.01 ± 0.10	.734	0.03 ± 0.10	.382				
Abdelraouf et al., **2019***	BL-3	−0.31 ± 0.25	0.025	−0.07 ± 0.18	–			–		−36.5 ± 24.4 %	−0.9 ± 10.6 %	<.001	
	3–6	−0.06 ± 0.17!	0.822	0.04 ± 0.13						−11.8 ± 30.03 %	0.9 ± 8.9 %	.224	
	BL-6	−0.25 ± 0.26!	0.047	−0.03 ± 0.13						−45.0 ± 28.5%	−2.0 ± 11.4%	<.001	

Prospective studies														
Author	**Follow up**	**Vertical papilla gain (mm)**				**Gingival volume change (mm2)**				**BT area (%)**				
year	**(months)**	**Test**			**Control**	**Test**			**Control**	**Test**			**Control**	*p* Value
Singh et al., **2019*****		HA 1%	HA 2%	HA 5%	–	–			–	HA 1%	HA 2%	HA 5%	–	–
	BL	3.59 ± 0.93	3.85 ± 1.4	3.91 ± 1.81						0%	0%	0%		–
	1	3.09 ± 1.15	3.64 ± 0.85	3.16 ± 1.68						17%	0,10%	41,50%		–
	3	3.21 ± 0.79	3.64 ± 0.8	3.1 ± 1.6						18,80%	0,06%	42,90%		–
	6	3.43 ± 0.85	4.14 ± 1.2	3.2 ± 1.6						14,20%	0,02%	39,80%		–
		p Value	Pvalue.	*p* Value										
		0.004	0.125	0.001										
Turgut et al., **2020**		–			–	Maxilla	Mandible		–	Maxilla	Mandible			
	BL					0.31 ± 0.05	0.25 ± 0.05	<0.001		0%	0%	.152		
	3					0.14 ± 0.03	0.11 ± 0.02	<0.001		54.21 ± 6.75%	57.24 ± 6.26%	.213		
	12					0.09 ± 0.02	0.07 ± 0.01	.002		73.22 ± 5.60%	71.40 ± 3.32%	.543		
	24					0.07 ± 0.02	0.06 ± 0.01	.024		79.35 ± 5.86%	78.71 ± 4.04%			
Alhabashneh et al., **2020**	BL	2.14 (2.01, 2.26) <0.001			–					–				
	3 weeks	1.97 (1.86, 2.09)												
	3	1.31 (1.16, 1.47)												
	6	1.52 (1.34, 1.71)												

Case Series											
Author	**Follow up**	**Vertical papilla gain (mm)**			**Gingival volume change (mm2)**			**BT area (%)**			
year	**(months)**	**Test**	**Control**	*p* Value	**Test**	**Control**	*p* Value	**Test**	**Control**	*p* Value	
Becker et al., **2010**	6	–	–	–	–	–	–	91.07 ± 11.55%	–		
Mansouri *et al.* **2013**	3 weeks	–	–		–	–		3.38 ± 3.07%	–		
	3							29.52 ± 18.72%			
	6							47.33 ± 20.20 %			
Awartani et al., **2016**	BL	–	–		1.24 ± 1.84	–		59 ± 63 %			
	4				0.57 ± 0.93 < 0.0001						
	6				0.71 ± 0.74 < 0.0001						
Lee et al., **2016** **	BL-6	0.70 ± 0.29	–		0.21 ± 0.14	–		88.80 ± 19.42 %			
Ni J et al., **2019** **	BL	2.90 ± 1.30	–		1.355 ± 0.779	–		–			
	3	3.21 ± 1.20 p .015			1.043 ± 0.748 p .006						
	6	3.35 ± 1.11 p .001			0.994 ± 0.739 p .002						
	12	3.30 ± 1.11 p .004			1 ± 0.831 p .014						
Spano et al., **2019***	BL	3.62 ± 1.29 *	–		–	–		11.54 ± 12.11 %	–		
	6 weeks	1.75 ± 1 0.65						71.29 ± 14.84%.			
	6	1.75 ± 0.5						73.99 ± 21.69 %			

BL: Baseline HA: Hyaluronic Acid. BT: Black Triangle.

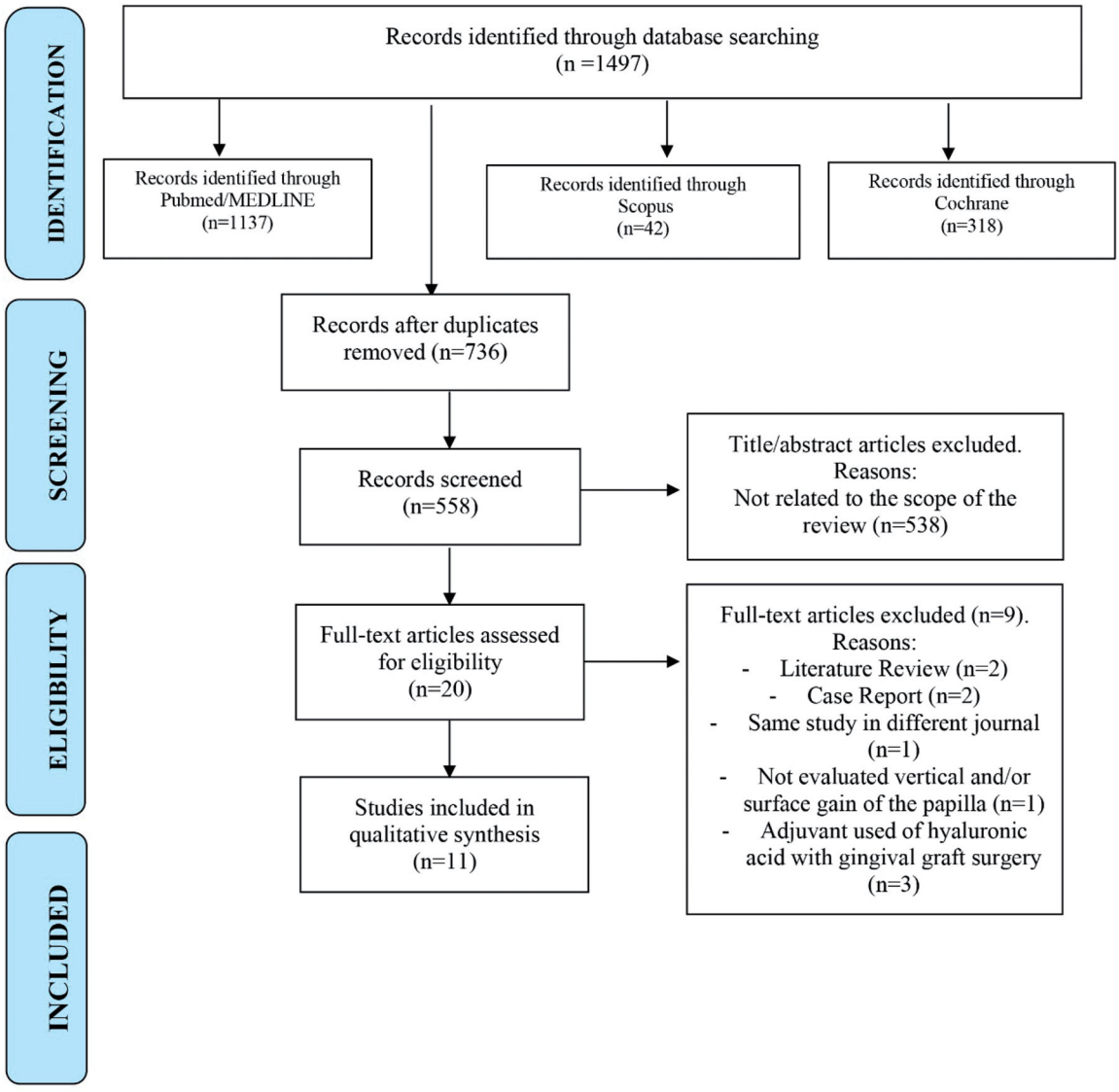

Figure 1. Flow diagram of the literature search, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Table 5. Studies quality assessment by means of the Joanna Briggs Institute scale.

	Quality of the studies was assessed by the Joanna Briggs Institute.										
Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Overall appraisal
Becker et al. (2010)	U	Y	N	N	Y	Y	N	Y	N	N	4
Mansouri et al. (2013)	Y	Y	N	N	Y	Y	N	Y	Y	Y	7
Awartani et al. (2016)	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8
Lee et al. (2016)	Y	Y	N	N	N	Y	N	Y	Y	Y	6
Ni J et al. (2016)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	9
Spano et al. (2019)	Y	Y	Y	Y	Y	Y	Y	U	Y	N	8

Controlled clinical trials

According to the 7 domains for assessing risk of bias of the Cochrane Collaboration's tool, we determined that the 4 controlled trials included in this systematic review had high risk of bias (high risk of bias for 1 or more domain). Two of them had high risk of performance bias as the blinding of the clinicians could not be achieved because HA and control group presented different consistency [26,28] and different resistance to injection [28]. The other two studies had high risk of selection bias as no randomisation was performed [30,32] and no allocation concealment was made [32]. Meanwhile, Turgut et al. study [32] had high risk of performance bias as there was no blinding, and high risk of detection bias because the same operator performed the injections and the outcomes assessment (Figure 2).

Prospective cohort studies

According to the NOS scale, one study scored 4 points [30], other six [32] and finally the last included study obtained 7 points. These obtained scores reflect an adequate quality among the included the assessment (Table 6).

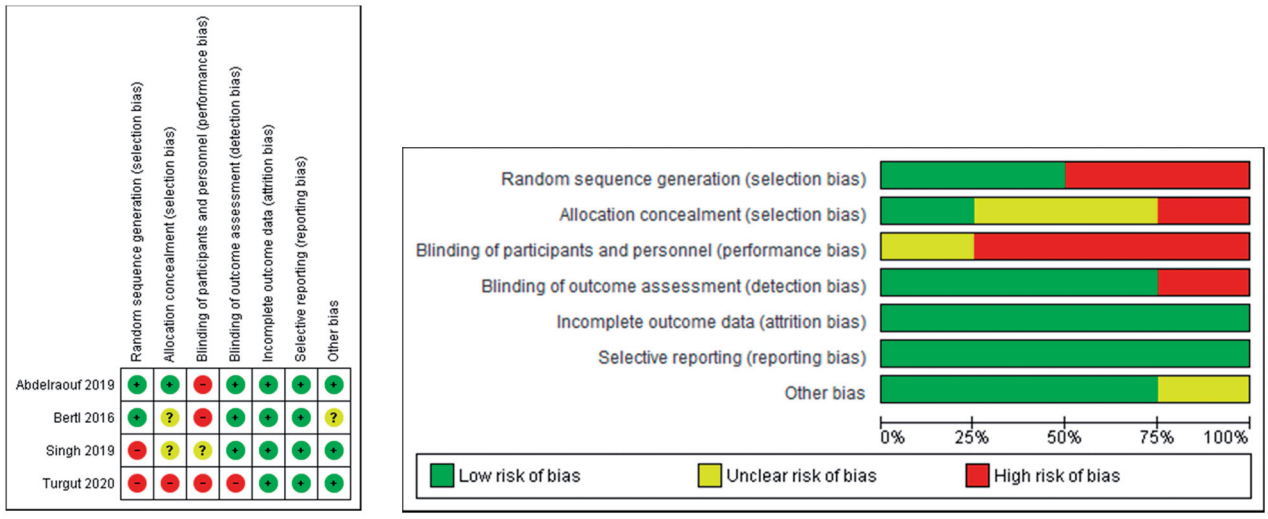

Figure 2. 'Risk of bias's summary: review authors' judgements about each risk of bias item for each included study and bias item presented as percentages across all included studies.

Table 6. Quality assessment of the studies using the Newcastle–Ottawa scale.

				Newcastle Ottawa Scale			
Author	Year	Study design	Follow-up	Selection	Comparability	Outcome/Exposure	Total
Singh et al.	2019	Prospective cohort	6	***	-	*	4
Turgut et al.	2020	Prospective cohort	24	****	*	*	6
Alhabashneh et al.	2020	Prospective cohort	6	****	*	**	7

Synthesis

Only 2 studies, which reported mean ± standard deviation (SD) of PT-CP (in mm) in both HA and control groups [26,28]. The other studies included in this systematic review did not have a control group. However, both these studies [26–28] performed different administration techniques and used different methods to evaluate the papilla gain. To perform this meta-analysis, the data was considered as heterogenous. Hence a meta-analysis could not be performed.

Data synthesis

Papilla evaluation score

Five studies [25,28,29,31,33] used Nordland & Tarnow Classification [2]: four of them [25,28,29,33] included Class I and II defects, while one study included Class I, II and III defects [29]. Two studies [26,32] used the Modified Papilla Index Score (MPIS) [33], and one study [30] classified the papilla defects according to Cardaropoli Classification [34]. Four studies did not specify the papilla classification [23,24,27]. Additional information on the applied scores is listed in Table 3.

HA injection intervention

Three of the selected studies did not specify the use of local anaesthesia [24,25,27]. Eight studies performed a previous local anaesthesia before HA injection [23,26,28–33]. Eight studies used an injection of 0.2 ml hyaluronic-based gel [23–25,27,30–33] and 3 studies used a concentration of 0.1 ml hyaluronic-based gel [26,28,29]. Only one study [31] performed an incision on the alveolar mucosa above the deficient papilla. Three studies performed 3 injections per session [26,32,33], meanwhile 8 studies only performed one injection [23–25,27–31]. Some studies repeated number of sessions: 5 times [27], 3 times [24,25,28–30,32], between 2–3 times [23], 2 times [26] or one time [31,33]. Eight studies [23–25,27–29,32,33] repeated sessions in 3 weeks-intervals, one study [26] after 4 weeks, and one study [30] did it at 2nd week and 3rd week after the baseline. The results of Spano et al. [31] did not specify when they repeated the injections.

Regarding the injection technique, five studies injected the filler 2–3 mm apical to the PT [23,25–28], two of them at 2–3 mm coronal to the PT [24,30] and three at the base of the deficient papilla [29,31,33]. Two studies [26,32] performed a 3 injection-technique filling. One study [32] described a technique with 3 injections at the papilla forming an equilateral triangle with the adjacent teeth. Another 3 injection-technique was described by Bertl et al. [26]: firstly, creating a reservoir in the mucosa above the mucogingival junction, secondly injecting 2–3 mm apically to the tip of the deficient papilla and finally into the attached gingiva/mucosa just below the base of the deficient papilla. Post-operative instructions varied among 6 studies [24,25,28,31–33], being the most common recommendations no brushing within first 24 h and extreme oral hygiene after the procedure. Five studies did not specify any recommendations [23,26,27,29,30]. Details of the clinical procedures are reported in Table 3.

Papilla measuring tools

Ten studies evaluated the papilla changes with photographs [23–33], two studies used a morphometric analysis with

periodontal probe calibration and a stent cast reference to evaluate the vertical papilla gain [28,30]. Four studies evaluated with an image software analysis [26,27,29,33] and only one reported the papilla height changes with a periodontal probe [31]. No data are available for the vertical augmentation in four studies [23–25,32]. Seven studies employed digital programs such as pixel software's [23,24,27] and image software analysis [25–28,32] for papilla surface changes or BT reduction. For the evaluation of the BT reduction, two studies [26,32] performed intraoral scans. Finally, the volume papilla changes were not evaluated in four studies [29–31,33].

Main papilla findings

The interdental papilla loss reconstructions were evaluated in 11 studies and 7 studies evaluated the vertical papilla gain [26–31,33]. Five studies recorded the papilla augmentation in mm^2 [25–27,29,32] and 8 studies described the papilla gain/BT reduction in percentage [23–25,30–32]. These results are summarised in Table 4.

Vertical papilla gain

The papilla augmentation evaluation method differed among studies. Three studies evaluated PT-CP distance in mm [26,28,31]. Three studies described the change of the height of the deficient papilla with periodontal probing [27,29,33]. Only one study described the vertical papilla gain with the distance between the apical margin of the stent and the tip of the papilla [30]. For the PT-CP distance, Abdelraouf et al. [28] observed a statistically significant reduction from baseline to 3 months ($p < .001$), and from baseline to 6 months ($p = .047$) in HA group when compared to control group, respectively. However, authors were not able to reveal significant difference in the vertical papilla gain [25,29]. Ni et al. [29] concluded that the height of the gingival papilla was increased by 0.311 mm, 0.45 mm, and 0.4 mm at 3 ($p = .015$), 6 ($p = .001$), and 12 ($p = .004$) months follow-ups, respectively. In addition, Lee et al. [27] did not report a significant difference in the height of the papilla at 6 months follow-up.

The results of Singh et al. [30] study described the vertical papilla change with distance from stent cast to PT. In addition, this was the only study that compared three different concentrations of HA, showing that groups with a 1 and 5% of HA showed a significant papilla gain ($p = .04$) (p .001) of the PT-CP than 2% group. According to Alhabashneh et al. [33] there was a significant reduction from baseline from 2.14 mm to 1.52 mm at 6 months follow up.

Gingival volume changes (mm^2)

Three studies evaluated gingival volume changes in mm^2 [25,26,32]. The clinical study between 6- and 24-months follow-up [26] showed no differences in the papilla filling when compared HA with CG at any observation time or within groups over time. Otherwise, Awartani et al. [25] and Turgut et al. [32] studies obtained statistically significant ($p < .0001$) increase of the papilla at 6 months follow-up.

Black triangle changes (%)

Nine studies described the percentage of the BT area (%) [23–25,27–30,32,33]. Regarding the results, another way to measure changes in the papilla were the percentage of papilla fill, while others reported the BT reduction. Several studies established a mean papilla percentage filling from 73 to 92% at 6 months [23,27,31,32]. On the other hand, the BT reduction varied from 19 to 47% at 6 months follow-up [24,25,28,29,31]. Bertl et al. [26] and Abdelraouf et al. [28] studies showed no statistically significant results between HA and control groups. Moreover, according to Alhabashneh et al. [33] there was a statistically significant mean difference in BT reduction between baseline and 6 months (MD = 0.62, 29% reduction, p-value < 0.001).

Adverse effects

Only 5 studies reported complications [25,26,29,30,33]. Pain, swelling was recorded in 50% of the patients. Authors described that bleeding were the most common complications during the procedure some injection sites, which was managed by application of pressure on the wound. In only one case [29], a pain- less granuloma was after the first injection, but it was not detectable at the 3-month follow-up. VAS scale related with the papilla injection pain was judged as acceptable by the patients in 4 studies [26,28,31,33] with values between 30–62%.

Discussion

The aim of the present study was to systematically analyse the available literature on the use of HA by injection to restore the interproximal papilla. Based on the obtained results, 11 studies [23–33] were included. When focussing on the results reported from case series, several articles reported no-differences in term of PT-CP distance n [28–31] or the papilla fill reduction [25,26,32]. Finally, most of the studies showed a BT reduction with a percentage range between 19 and 47% [24,25,28–30].

Interproximal bone loss and the consequent loss of the interdental papilla is one of the most common and challenging problems in daily clinical practice [35,36]. Therefore, it is important to reconstruct the papilla in order to improve aesthetics and function, avoiding food impaction and protecting deep periodontal tissues [5,23]. One aspect that has to be underlined is that the majority of the treated cases presented no or limited interproximal attachment loss which might be clinically assimilated to Miller' s Class type I and II recessions: therefore, no indications can be drawn on the application of HA by injection to restore Miller's Class III defects. On the other hand, recent data support the use of HA to obtain full root coverage of Miller's Class I [37] and Class II [38] with a coronal advanced or modified tunnel technique flap, as a predictable and safe method reducing patient's discomfort.

The interdental papilla presents some histological differences to the interproximal peri-implant papilla mainly related to the absence of the periodontal ligament: therefore,

although it is true that the same cell lines exist in the peri-implant tissues, the absence of the vascular component associated with the periodontal ligament means that there are limitations in the response of the peri-implant tissues [39].

Despite the different proposed surgical interventions, half of the included studies reported post-operative complications up to 50%, making for the researchers extremely challenging to detect the best treatment modality to delivery HA. More specifically, in most of the cases, patients presented with moderate pain and swelling on the treated area that spontaneously healed within one week. A possible explanation to these events has been proposed by Bertl et al. 2016 who linked the post-operative swelling and edoema to 'the water attraction over time by the highly hygroscopic HY, exerted progressively an external vascular compression and at least partial occlusion of neighboring blood vessels'.

On the same topic, Ficho et al. have published a similar systematic review recently [40]. However, the systematic review by Ficho *et al* performed the database search over a very limited period of 2010 to 2016. Due to the limited data reviewed in this systematic review, the results appear to be skewed. The present systematic review has tried to perform a more extensive search of the database. This review has compared various different techniques and procedures for papillary fill with HA used till date.

The present systematic review is not free from limitations: first, only two RCTs with heterogeneity in the data hence we could not perform a meta-analysis; second, differences in the HA injection technique protocols were detected: in particular, some studies injected the filler 2–3 mm apical to the tip papilla [23,25–28,32], while other 2–3 mm coronal to PT [24,30], or at the base of the deficient papilla [31,35]. Moreover, the frequency of the injection varied consistently among studies: 6 studies reported the application of HA 3x, while 1 study stated that they performed the application only twice. Third, methodological differences in assessing papilla augmentation (i.e. photographs and morphometric analysis [24–31], photographs and a pixel software [23] or digital impressions with image analysis program [32] make comparison among studies difficult.

Conclusions

Within the limitations of this study, the presented results showed that repeated HA injections slightly increased the vertical papilla gain, papillary volume and reduction of the black triangle area with a follow-up ranged between 6 and 24 months. Nonetheless, adverse reactions such as pain and swelling have been reported. Further long-term and well-designed randomised clinical trials using standardised techniques are needed in order to confirm these findings. In addition, patient-reported outcome measures (PROMs) as well as aesthetics impairments caused by the different techniques used for papilla reconstruction should be further analysed.

One sentence summary

Hyaluronic acid might be clinically used to re-create the interproximal lost papilla.

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Disclosure statement

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