Is periodontal phenotypic modification therapy beneficial for patients receiving orthodontic treatment? An American Academy of Periodontology Best Evidence Review

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Running title: Phenotypic modification therapy for orthodontic patients

One sentence summary: Periodontal phenotypic modification therapy (PhMT) via corticotomy-assisted orthodontic therapy (CAOT) combined with simultaneous hard tissue augmentation (PhMT-b) provide clinical benefits to orthodontic patients

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MeSH key words: orthodontics, periodontium, phenotype, evidence-based dentistry, systematic review

Abstract

Background:

Orthodontic treatment can greatly impact the periodontium, especially in dentitions with a thin periodontal phenotype. Orthodontic tooth movement can result into iatrogenic sequelae to these vulnerable anatomic conditions, such as development and exacerbation of bony dehiscence or fenestration defects, which can manifest lost of periodontal support and gingival recession (GR). This systematic review aimed to investigate whether periodontal phenotypic modification therapy (PhMT) involving in hard tissue augmentation (PhMT-b) or soft tissue augmentation (PhMT-s) has clinical benefits for patients undergoing orthodontic treatment.

Methods: An electronic search was performed in two major databases for journals published in English language from January 1975 to January 2019 and hand search of printed journals were also screened to identify human clinical trials reporting clinical and radiographic outcomes of patients receiving orthodontic treatment with or without hard and soft tissue augmentation procedures. Data was extracted and organized into tables for qualitative assessment.

Results: Eight studies were identified evaluating the outcomes of PhMT in patients undergoing orthodontic therapy. Six studies evaluated patients receiving PhMT-b via corticotomy-assisted orthodontic therapy (CAOT) and simultaneous bone augmentation while the other two received PhMT-s prior to tooth movement. No studies investigated PhMT-b alone without CAOT and most studies focused on the mandibular anterior decompensation movements. There was high heterogeneity in the study design and inconsistency of the reported outcomes; therefore, a meta-analysis was not performed. Evidence, at this moment supports CAOT with hard tissue augmentation enhanced tooth movement. However, only two studies provided indirect evidence to support CAOT reduced the overall treatment time compared to conventional orthodontic treatment. No periodontal complications or evidence of severe root resorption were reported for both groups. Four studies provided radiographic assessment of the PhMT-b and demonstrated increased radiographic density or thicker facial bone after the treatment. Two studies reported an expanded tooth movement. One study reported an increase in keratinized tissue width (KGW) post CAOT plus PhMT-b while another study

with a 10-year follow-up showed a lower degree of relapse using the mandibular irregularity index when compared to conventional tooth movement alone.

Two studies examined the effect of PhMT-s prior to orthodontic treatment. Unfortunately, no conclusions can be drawn because of the limited number of studies with contradicting outcomes.

Conclusions: Within the limited studies included in this systematic review, PhMT-b via particulate bone grafting together with CAOT may provide clinical benefits such as modifying periodontal phenotype, maintaining or enhancing facial bone thickness, accelerating tooth movement, expanding the scope of safe tooth movement for patients undergoing orthodontic tooth movement. The benefits of PhMT-s alone for orthodontic treatment remain undetermined due to limited studies available. PhMT-b appears promising and with many potential benefits for patients undergoing orthodontic tooth movement. There is a need for higher quality of randomized controlled trials (RCTs) or case-control studies with longer follow-up to investigate the effects of different grafting materials and surgical sites other than mandibular anterior region.

1 Introduction

Orthodontic tooth movement and the periodontium have a dynamic and co-dependent relationship[1-7]. It has been documented that about 20-35% of the patients may develop facial gingival recession (GR) 2-5 years after orthodontic treatment.[8] According to the 2017 world workshop and previous consensus reports from the American Academy of Periodontology (AAP), a higher incidence of bony dehiscence and GR could be observed in teeth surrounded by thin periodontal phenotypes or if orthodontic forces were applied to move dentition outside of the alveolar process such as arch expansion [9, 10]. Therefore, it is important to carefully assess dentoalveolar bone and soft tissue conditions prior to tooth movement [11-13]. With the advancement of cone-beam computed tomography (CBCT), clinicians are now able to assess dentoalveolar deficiencies and alveoloskeletal discrepancies before the inception of tooth movement and scrutinize the boundary conditions with a high level of accuracy[3]. Patients who pose higher risks to periodontal breakdown from orthodontic tooth movement may warrant phenotypic modification therapy involving in hard (PhMT-b) and soft tissue augmentation (PhMT-s) [11-13].

Surgical procedures have been introduced to assist orthodontic treatment, such as periodontally accelerated osteogenic orthodontics (PAOO)[14-15], surgically-facilitated orthodontic therapy (SFOT)[16-18] or corticotomy-assisted orthodontic therapy (CAOT)[19-20]. These procedures involve corticotomy surgery and decortication of the dentoalveolar complex with or without particulate bone grafting. The literature has shown that corticotomy and dentoalveolar bone decortication can accelerate tooth movement and has the potential to reduce the overall treatment time associated with orthodontics.[18-20] However, little is known about the clinical benefits of transforming a thin to thick periodontal phenotype by integrating hard or soft tissue augmentation procedures, a technique known as phenotypic modification therapy (PhMT).

The aim of this systematic review was to assess the clinical benefits of performing periodontal PhMT on patients who are undergoing orthodontic treatment.

2 MATERIALS AND METHODS

The text of this systematic review was structured in accordance with guidelines from PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [21].

2.1 Population, Intervention, Comparison, Outcome (PICO) question

The focused question of this systematic review was: "Does periodontal phenotypic modification therapy (PhMT) involving in hard (PhMT-b) or soft tissue (PhMT-s) augmentation benefit patients undergoing orthodontic treatment?"

Population: Patients who are undergoing orthodontic treatment.

Intervention: PhMT via bone or soft tissue augmentation

Compare: No PhMT via bone or soft tissue augmentation

Outcomes: Clinical and radiographic outcomes that are pertinent to periodontal and orthodontic treatments were assessed. Periodontal outcomes included probing depth (PD), gingiva recession (GR) and keratinized tissue width (KTW). Radiographic assessment included bone density, bone thickness, root length. Orthodontic outcome measurements evaluated the duration of the orthodontic treatment, tendency of relapse after the treatment, labial movement of incisor edge and incisor mandibular plane angle.

2.2 Type of studies and participants (inclusion and exclusion criteria)

Randomized controlled trials (RCTs), controlled clinical trials (CCTs), case control or cohort studies published in English language from January 1975 to January 2019 were screened. Studies were considered eligible for inclusion if they specifically involved the following: a) Studies with adult or adolescent patients who had orthodontic treatment with post-treatment follow-up; b) PhMT-b or PhMT-s before or during orthodontic treatment; and c) reported clinical outcomes, including periodontal and radiographic parameters (PD, GR, KTW, bone density, bone thickness), orthodontic outcome (duration of the orthodontic treatment, tendency of relapse after the treatment, labial movement of incisor edge and incisor mandibular plane angle) and other complications (root length) after the therapy. Case reports or case series with no comparison to PhMT were excluded. Studies missing reports on the above-mentioned periodontal or orthodontic outcome measurements will be further excluded. Editorials, letters or comments, non-English citations, animal/in vitro studies and review articles were not considered eligible in this review.

2.3 Search strategy

Two independent examiners (CWW and SHY) conducted the literature search for articles published in English language up to and including January 2019 in 2 major electronic databases: 1) PubMed; 2) Cochrane Library. It consists of a checklist and a flow diagram. Comprehensive search strategies were established to identify studies for inclusion in the systematic review:

1) "orthodontic" [All fields] AND "corticotomy" [All fields]; 2) "orthodontic" [All fields] AND "grafting" [All fields]; 3) "orthodontic" [All fields] AND "accelerated" [All fields] 4) "orthodontic" [All fields] AND "augmented" [All fields] 5) "orthodontic" [All fields] AND "osteogenic" [All fields]. The screening in such databases was limited to "Case reports" OR "Clinical study" OR "Clinical Trials" AND "Humans" subjects. In addition, a search for references in the included papers was performed. Finally, hand search (January 2018 up to January 2019) was carried out in the following journals to identify relevant studies, including *Journal of Periodontology*, *Journal of Clinical Periodontology, International Journal of periodontics and Restorative Dentistry, American Journal of Orthodontics and Dentofacial Orthopedics, The Angle Orthodontist*. For grey literatures, Google Scholar was utilized to search for any articles not included in the major database.

2.4 Literature selection and data extraction

Two independent reviewers (CWW and SHY) conducted the initial screening of the literature and abstract. Potential articles were scrutinized in full-text for their eligibility and included after discussion. When there was a disagreement in terms of the eligibility, a third reviewer (HLW) was consulted for final decision. Data related to the outcomes of interest as described under PICO question were extracted from the included studies and organized in the table for subsequent qualitative analyses.

2.5 Assessment of methodological quality

The criteria used to evaluate the quality of the selected RCTs were modified from the RCTs checklist of the Cochrane Center and the CONSORT (Consolidated Standards of Reporting Trials) statement[22], which provided guidelines for, sequence generation, allocation concealment method, masking of the examiner, address of incomplete outcome data and free of selective outcome reporting. The degree of bias was categorized as low risk if all the criteria were met, moderate risk when only one criterion was missing, and high risk if two or more criteria were missing.[22-24] Two independent reviewers (CWW

and SHY) evaluated all the included articles. On the other hand, for non-RCTs, the New Castle Ottawa Scale (NOS) was used to rank risk of bias of included studies.[24]

3 RESULTS

The screening process can be found in Figure 1. Initial screening of electronic databases yielded a total of 1689 articles. Additionally, 4 more articles were found through manual screening. After removal of unrelated and duplicated studies, a total of 168 titles and abstract were evaluated. Twenty-one articles were selected for full-text evaluation after screening of titles and abstracts. Thirteen articles were further excluded due to less than three subjects reported in the article. The detailed reasons for exclusion can be found in Table 1. A total of 8 articles were included and analyzed in this systematic review. The main features and conclusions of the included studies are summarized in Table 2 (PhMT-b) and Table 3 (PhMT-s).

Significant heterogeneity between publications in terms of study designs, methods of measurement and reported outcomes prevented the quantitative synthesis of the included studies and consequently a meta-analysis could not be completed. Therefore, a qualitative descriptive analysis of the reported outcomes was performed and systematically reviewed in the forms of tables.

3.1 Features of the included studies

The characteristics of the 8 included articles are summarized in Tables 2 and 3.[12, 25-31] They included 2 RCTs[25, 26] and 6 retrospective studies (3 cohort studies)[12, 27-31]. The studies are mainly divided into two groups based on their approaches with PhMT-b or PhMT-s. 6 studies utilized bone grafting in combination with CAOT[25-30] during orthodontic treatment. No studies evaluated bone grafting alone without CAOT. Two studies used autologus free soft tissue grafts at the area of interest[12, 31].

The follow-up periods of the studies ranged between 2.5 months to 10 years. Most of the studies reported patient numbers and the majority of the PhMT surgeries were performed at the mandibular anterior region[12, 25, 26, 28-31]; except for one study that the surgical site was not clearly indicated.[27]

The outcome assessment methods of the included studies varied greatly, only 2 studies evaluated PD change[25, 26]. The majority of studies reported radiographic examinations such as periapical radiographs, CBCT or lateral cephalograms to evaluate bone thickness, bone density and the

movement of teeth after orthodontic treatment with the augmentation procedures[25-27, 29-30]. One study used dental casts to evaluate mandibular irregularity index, which is an indices for relapse of the lower anterior teeth 10 years after the completion of orthodontic treatment[28]. Most of the included studies reported the mean orthodontic treatment time[25, 26, 29] or the decompensation time prior to orthognathic surgery[30].

3.2 Bone grafting augmentation and treatment outcome (Table 2)

For PhMT-b studies, all studies combined CAOT, and most of the articles provided details to the surgical techniques and materials that were utilized. Two studies used bioactive glass[25, 26] while other studies used deproteinized bovine bone mineral (DBBM) materials[26-30].

The studies with PhMT-b and CAOT can be further divided into two subcategories: 1) studies with PhMT-b along with CAOT ~~plus bone grafting~~ compared to CAOT alone[25-27]; 2) studies with PhMT-b along with CAOT ~~plus bone grafting~~ compared to conventional orthodontic treatment[28-30].

In terms of periodontal findings, only two studies reported PD and GR and they found no further recession with shallow PD between 1-3 mm. There was no statistically significant difference between the CAOT with or without PhMT-b[25, 26]. No studies evaluated gingival thickness (GT), only one article reported an average increase of 0.78 mm KTW after PhMT-b versus a loss of 0.38 mm KTW with no PhMT-b[29].

With regards to radiographic outcome, 2 studies reported increased 15-30% bone density after PhMT-b with DBBM or bioactive glass.[25, 26] Two other articles demonstrated an 0.5-2 mm increase of labial bone thickness in the mandibular incisors [27, 30]. One study compared CAOT along with PhMT-b ~~plus bone grafting~~ to conventional orthodontic treatment and found the CAOT along with PhMT-b had less alveolar bone crest resorption while conventional orthodontic treatment resulted in a 4 mm crestal bone loss. [30]

Root resorption is also of a concern occurring iatrogenically from orthodontic tooth movement. Two studies reported root length maintained (10-12mm) after PhMT-b [25, 26], while one study showed mild apical root resorption (-0.6mm) in both CAOT with or without PhMT-b groups[30].

Additionally, PhMT-b might allow for expanded tooth movement opportunities. This is demonstrated by less proclination of the teeth during decompensation [29-30] and an additional 1.2 mm labial movement of the mandibular incisors when compared to conventional orthodontic treatment[30].

In terms of the treatment time duration, only two cohort studies reported CAOT and PhMT-b reduced treatment time from 22 months (conventional orthodontic treatment) to 7 months [29]; and 10.9 months (pre-orthognathic surgery treatment time) to 8.7 months[30]. Other studies described accelerated orthodontic tooth movement but failed to provide direct comparison data between CAOT and conventional orthodontic treatment[25-26]. Two studies reported similar treatment time with a mean of 15-17 weeks with or without PhMT-b[25, 26], indicating the accelerated tooth movement is primarily a result of the corticotomy injury itself and the creation of a transient demineralized bone matrix.

The mandibular irregularity index scores crowding[32], and it is an established method to track the relapse of the mandibular anterior teeth post-orthodontic treatment. PhMT-b might enhance the long-term stability of the teeth as one study reported lower irregularity index of the mandibular anterior teeth 10 years after the completion of orthodontic tooth movement.[28]

Overall, the included studies supported CAOT along with PhMT-b during orthodontic treatment could augment the phenotype of the dentoalveolar bone complex and increase KTW, especially at the mandibular incisors. Moreover, CAOT along with PhMT-b may shorten the total treatment time and limit relapse.

3.3 Soft tissue grafting augmentation and treatment outcome (Table 3)

Only 2 articles were identified for this review pertaining PhMT-s prior to or during orthodontic treatment. Both studies utilized autologous free gingival grafts [12, 31]. One study reported no further recession or bone loss could be found after PhMT-s [12]. The other article reported phenotype transformation and showed that pre-orthodontic PhMT-s yielded similar post-orthodontic gingival recession and retraction of mandibular incisor might help reverse the recession[31].

There are no published studies of PhMT combining both hard tissue and soft tissue augmentation.

3.4 Risk of bias of assessment

The results of risk of bias assessment for the included two RCTs[25, 26] were summarized in Table 4. It showed that there is a higher risk in blinding of participants and personnel (performance bias) and data reporting (reporting and attrition bias). In addition, 6 non-RCTs (case control of cohort studies) were evaluated through Newcastle-Ottawa Quality Assessment Scale and the assessment can be found in Table 5 [24]. Four out of six studies only scored less than 4 stars indicating significant risk of bias.

4 DISCUSSIONS

It is estimated that 75% of the population in the United Stated have some degree of malocclusion[33] and that an ever increasing number of adults are interested in having orthodontic treatment as part of the comprehensive dental care[34]. In 2013, Keim et al. reported that approximately 23% of the patients receiving orthodontic treatment are adults[35]. It is widely recognized that most of the adult population have thin periodontal phenotypes with less than 1 mm facial bone.[36-38] Those patients may be associated with a higher risk in developing iatrogenic sequela from tooth movement. Therefore, it is important that adult patients who are interested in receiving orthodontic treatment to have a comprehensive clinical and radiographic assessment of their periodontium for risk stratification and management. Patients with a thin periodontal phenotype may warrant periodontal phenotypic modification (PhMT) via hard or soft tissue grafting to optimize periodontal/bone conditions in preparation for optimal orthodontic tooth movement. The purpose of this review was to present the best evidence in the literature regarding the benefits of PhMT-b and/or PhMT-s-for patients undergoing orthodontic treatment.

Most of the included studies utilized PhMT-b during decompensation of mandibular anterior teeth, combining CAOT (via interradicular corticotomy) with hard tissue grafting of synthetic or DBBM materials over the dentoalveolar complex. In terms of the outcome of PhMT-b, the primary methods of evaluating bone thickness in the studies were CBCT or lateral cephalograms. Results showed CAOT with PhMT-b could limit crestal bone remodeling or achieved thicker hard tissue dimensions compared to non PhMT-b treated groups. Those results supported the effectiveness of PhMT-b prior or during orthodontic treatment to maintain periodontium in limiting crestal bone remodeling and reducing dehiscence defects[27, 30]. However, it is important to keep in mind that DBBM is much more

radiopaque and poses a very slow turnover rate. Without histological evaluation, we cannot conclude that true bone regeneration or construction of a vascularized functional matrix resulted despite the findings from the radiographic and clinical presentation of a thicker phenotype. However, the stability of such augmented tissue is in need of long-term follow up and evaluation.

Based on case-control studies and case series, PhMT-b supported an increased scope of incisor tooth movement [29-30]. The anatomic limits of orthodontic tooth movement are set by the cortical plate of the alveolus at the level of the incisor apices and may be regarded as the "orthodontic walls"[39] or, more recently, with a contemporary synonym of "orthodontic boundary conditions"[40]. A previous review article presented PCT cases and evaluated the scope of tooth movement, and the authors concluded the anterior incisor relationship can be expanded beyond Proffit's envelope by an average of 2-fold[41,42]. However, the predictability of such approach should be evaluated on an individual basis and caution should be taken when applying numbers to actual patient care.

Another important dimension in orthodontic therapy warranting consideration is the contemporary management of the transverse maxillary deficiency. Currently, there is no controlled study assessing the ability of alveolar augmentation via particulate bone grafting to facilitate dental arch expansion. This is particularly important as the trends for extraction – retraction orthodontia is decreasing in the wake of oropharyngeal airway considerations and the possible benefits of optimizing oral cavity volume for anterior tongue posturing[43].

CAOT and PhMT-b have a potential to reduce the level of orthodontic relapse, which was demonstrated by the mandibular irregularity index over a 10 year follow-up period.[28] This finding is consistent with a 10 year post retention study that reported teeth with thicker mandibular bone had a lower chance to relapse compared to teeth surrounded by a thinner cortical plates, regardless of the trabecular bone structure[44]. However, whether this observation is contributed by the CAOT alone or PhMT-b would require further investigation.

For root length preservation after orthodontic treatment, 2 studies reported preserved root lengths after orthodontic treatment[25, 26]. On the contrary, one study observed same level of root resorption when comparing CAOT and PhMT-b ~~bone grafting~~ to the conventional orthodontic treatment[30]. Currently,

there is insufficient evidence to support CAOT along with PhMT-b will prevent root resorption during orthodontic treatment.

Most studies that have conducted PhMT-b together with the CAOT during orthodontic treatment employed the concept of regional acceleratory phenomenon (RAP)[45], which is a transient burst of bone remodeling during healing that accelerates and facilitates orthodontic tooth movement. Tooth movement under the context of CAOT is physiologically different than conventional orthodontics alone. The fact that teeth are moving through a demineralized bone matrix for a transient period of time may be the answer to why an expanded scope of tooth movement can occur without an increase in pathologic sequelae. It was estimated that tooth movement rate could reach 2 to 4 times faster and last about 3-4 months after such surgery.[20, 46] Hence, PhMT-b may also induce trauma as a result of the surgery itself and therefore accompanies RAP effect. However, there is no study evaluating whether hard tissue alone would accelerate tooth movement or not.

Most of the included studies did not specify the timing of when the PhMT was performed. For the two studies involving PhMT-s[12, 31], surgery was performed prior to the orthodontic treatment; whereas PhMT-b with CAOT was typically performed during orthodontic treatment. This raises a critical question: For patients planning to receive orthodontic treatment, is it better to perform hard and soft tissue augmentation before, during, or after orthodontic treatment? And, if it depends on each patient and their individual condition, what are the specific indications? From the previous AAP best evidence review,[9] the recommendation is to perform gingival augmentation at teeth (1) with less than 2 mm keratinized tissue; and (2) if the tooth is expected to have significant labial tooth movement.[10] Although current studies were unable to provide a definitive answer on the best timing to perform PhMT, it is reasonable to suggest that augmentation prior to any labial tooth movement, especially in the presence of a thin phenotype or when there is less than 2 mm keratinized tissue. However, each case is unique and should be treatment planned on a case-by-case basis.

There are only 2 studies[12, 31] with PhMT-s alone included in this review. A preliminary systematic review on the indications and timing of soft tissue augmentation was previously published[47]. However, no conclusions could be drawn from the limited studies published to date. Available studies are primarily autogenous gingival grafts with limited information regarding the technique performed, whether frenum is presented or not, and the degree of phenotypic augmentation or root coverage that was achieved[12]. Another interesting observation is that PhMT-b with CAOT has been shown to

increase KTW in one study although the direct influence between the PhMT-b and KTW is not fully understand [29]. All the included studies had limited or no reporting on GT or KTW- an important outcome to evaluate periodontium, therefore, it is important for these indices to be reported in future studies.

The main limitations of this current systematic review are the limited number of well-controlled studies, restricted applications, inconsistent reporting of the clinical outcomes, and short-term follow-up visits. Additionally, it is not clear if some studies may have utilized clinical data from the same cohort of patient population. Future studies should explore the benefits of PhMT with arch expansion and comprehensive evaluation of clinical parameters with a detailed description of the surgical procedure and materials used. Long-term controlled clinical trail or case-control studies are needed to assess whether PhMT can positively affect the long-term stability of the periodontium and avoid bony dehiscence or recession after orthodontic treatment.

5 CONCLUSIONS

Based on the limited clinical studies in this review, periodontal phenotypic modification therapy via corticotomy with particulate bone grafting (PhMT-b along with CAOT) may provide clinical benefits of augmenting periodontal phenotype, accelerating tooth movement, expanding the scope of incisor movement, and enhancing post-orthodontic stability of the mandibular anterior teeth. The benefits of PhMT-s alone during orthodontic treatment remain undetermined because of the limited studies available. Long-term, prospective, randomized clinical trails with comprehensive and consistent reporting of the clinical outcomes are needed to consolidate higher level of evidence for stronger conclusions.

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Figure 1. PRISMA flowchart of the screening process in the different databases

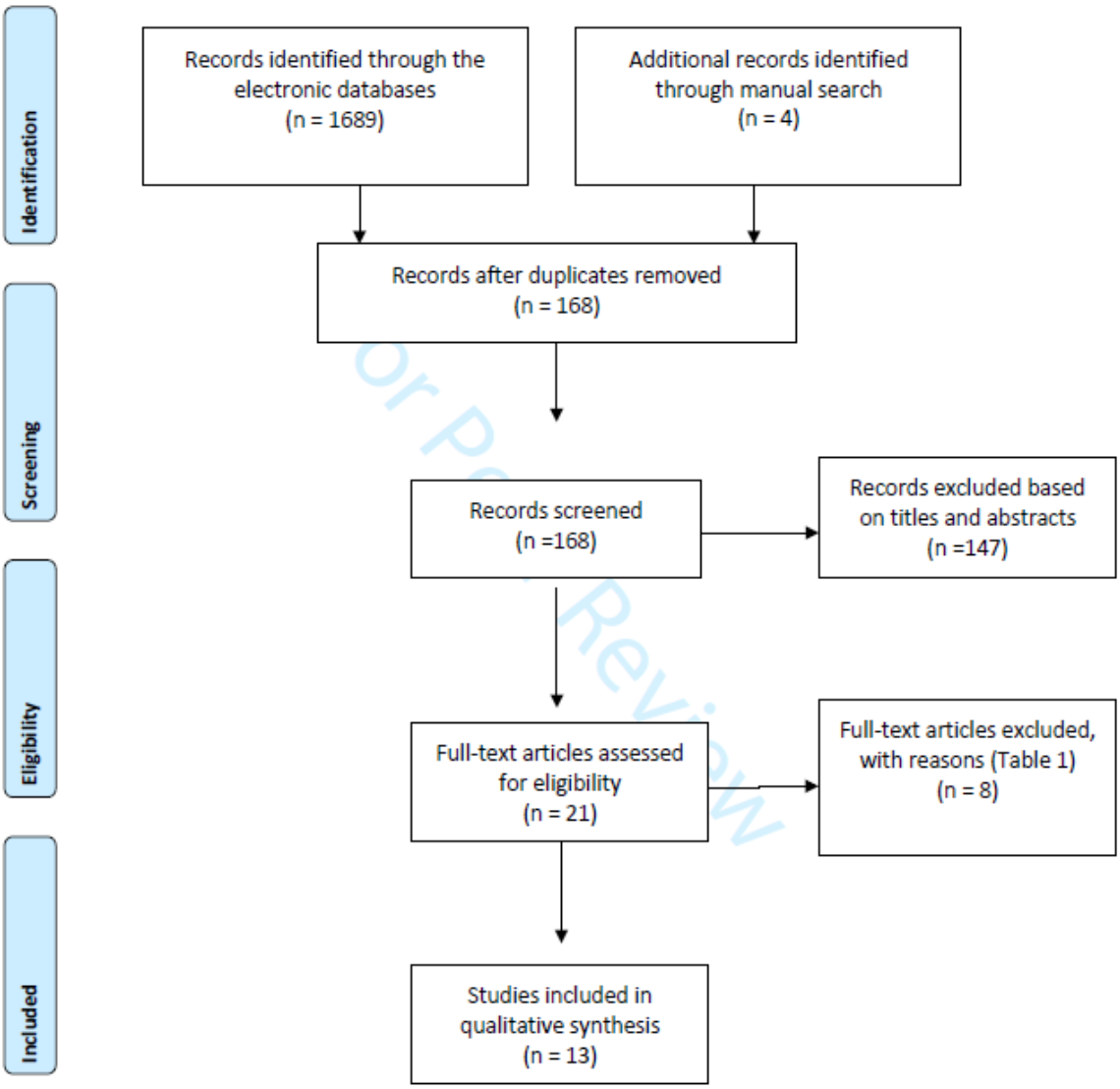

Table 1 Features of included articles of periodontal phenotypic modification therapy via bone augmentation (PhMT-b)

Author (year)	Study Design/ Duration	Tx case type (mean age)	Treatment groups and sample size (N)	Treatment location	Outcome			Conclusions (CAOT + bone grafting)
					Periodontal findings	Radiographic findings	Other findings	
CAOT + bone grafting vs. CAOT alone								
Shoreibah et al. (2012)[25]	RCT/ 6 months post-ortho tx	Class I (24)	T (10): CAOT+ Bioactive glass C (10): CAOT w/o graft	Mand Ant teeth	Mean PD (mm) change (NSSD): - T: -1.4 - C: -1.5	PA of 6 months post-ortho tx: Bone Density (%) (SSD): - T: +25.85 - C: -17.59 Root Length (mm) (NSSD): - T: -0.050 - C: -0.056	Pre-OGS tx time (weeks) (NSSD): - T: 16.7 - C: 17	Significantly increased alveolar bone density with no complications.
Bahamman (2016)[26]	RCT/ 9 months post-ortho tx	Class I (21)	T1 (11): CAOT + DBBM T2 (11): CAOT + bioactive glass C (11): CAOT	Mand Ant teeth	Mean PD (mm) before tx (NSSD): - T1: 1.57 - T2:	PA after tx: Bone Density (%) (SSD): - T1: +31.99 - T2:	Pre-OGS tx time (weeks) (NSSD): - T1: 16.8 - T2: 14.4	Increased bone density with no complications.

			w/o bone graft		1.56 - C: 1.54 Mean PD (mm) 9 months post-ortho (NSSD): - T1: 1.57 - T2: 1.56 - C: 1.54	+13.71 - C: -0.87% Root Length (mm) (NSSD): - T1: -0.04 - T2: -0.03 - C: -0.03	- C: 15	
Brugnami et al. (2017)[27]	Retrospective cohort study / 9 months	Class I & II (37)	T (13): CAOT + DBBM + collagen membrane C (7): CAOT w/o bone graft	NA	NA	CBCT: Bone Thickness (mm): *4mm from CEJ (SSD) - T: +0.86 - C: -0.24 *7mm from CEJ (SSD) - T: +0.95 - C: +0.26 *9mm from CEJ (SSD) - T: +1.39 - C: +0.7	NA	Minimize risk of marginal bone resorption and fenestration when moving teeth outside bony housing.
CAOT + bone grafting vs. conventional orthodontic treatment (Direct comparison with a								

control group)								
Makki et al. (2015)[28]	Retro-spective cohort study / T: 5 & 10 yrs C1: 5 yrs C2: 10 yrs C3: 10 yrs	Class NA T (35.3) C1(23.5) C2 (12.7) C3 (20.5)	T (43/39/22): CAOT + bone grafting C1 (23): conventional ortho + removable retainers C2 (55): conventional ortho + fixed retainers & no retainers C3 (15): no ortho	Mand incisors	NA	NA	Ortho tx time (months) (SSD between T&C): T: 6.8 C1: 22.7 C2: 28.5 Mand dental cast-Irregularity index scores change: (post ortho to final follow up) - T (5 yrs): +0.4 - T (10 yrs): +0.9 - C1 (5 yrs): +2.8 - C2 (10 yrs): +2.4 - C3 (10 yrs): +0.9	Reduced total treatment time. Enhanced stability of the post-ortho mand irregularity index.

Wilcko et al. (2015)[29]	Case control/ 16-19 months	Class NA (29.9)	T (35): CAOT + bone grafting C (35): conventional ortho	Mand Ant teeth	KT height (mm) (SS) - T: 3.52→4.3 (+0.78) - C: 3.24→2.86 (-0.38)	Lat ceph: IMPA (SS): - T: 94° → 96° - C: 99° → 100°	Ortho tx time (months) (SSD): - T: 7.1 - C: 22.1	Reduced total treatment time. Resulted in a significant increase in keratinized tissue height.
Ahn et al. (2016)[30]	Retro-spective cohort study / till OGS	Class III T (23) C (21)	T (15): CAOT + DBBM C (15): conventional ortho	Mand Ant teeth	NA	CBCT & Lat ceph: CEJ – alveolar crest distance (mm) (SSD): - T: - 0.56 (5.59→ 5.03) - C: + 3.95 (2.74→ 6.7) Labial Bone Thickness (mm): *Crestal - T: - 0.11 (0.55→ 0.44) - C: -0.43 (0.67→ 0.24) *Mid-root	Pre-OGS tx time (months) - T: 8.7 - C: 10.9	Increased labial movement of incisor edge. Limit crestal bone remodeling. Good adjunctive for ortho treatment in skeletal Class III patient.

						(SSD) - T: + 0.35 (0.3→ 0.65) - C: 0.24 (0.43→0. 19) *Apex (SSD) - T: +1.33 (0.41→1. 74) - C: +0.1 (0.55→ 0.65) Labial movemen t of incisor edge (mm) (SSD): - T: 2.35 - C: 1.14 IMPA (°)(SSD): T: 78 ° → 86 ° C: 78 ° → 84 ° Root Length change (NSSD): - T: - 0.6mm (12.1→		

						11.5mm) - C: -0.67mm (12.67→12mm)		

Ant= anterior; C= control group; CAOT= corticotomy-assisted orthodontic treatment; CBCT= cone-beam computed tomography; DBBM= deproteinized bovine bone mineral; IMPA= incisor mandibular plane angle; KT= keratinized tissue; L= lingual; Lat Ceph= Lateral cephalograms; Max= maxillary; Mand= mandibular; NA= Not available; NSSD= no statistically significant difference; OGS= orthognathic surgery; Ortho= orthodontics; PA= periapical radiographs; PD= probing depth; Perio= periodontal; Pt= patients; RCT= randomized clinical trial; SSD= statistically significant difference; T= test group; Tx= treatment; w/o= without; yrs= years

Table 2 Features of included articles of periodontal phenotypic modification therapy via soft tissue augmentation (PhMT-s)

Author (year)	Study Design / Duration	Tx case type (mean age)	Treatment groups and sample size (N)	Treatment location	Outcome			
					Periodontal evaluation	Radiographic and other findings	Other findings	Conclusion
Maynard and Ochsenbein (1975)[1,2]	Retro-spective/ 6 years	Children age 4-16 y/o need orthodontic treatments (8.8)	T (19): autogenous gingival graft in patients with <1mm of	Mostly mandibular ant teeth	12-19% children between had mucogingival problems requiring	NA	NA	Autogenous gingival graft is recommended in patients with insufficien

			attached gingiva C (81): no treatment		therapy Autogenous gingival graft increases keratinized gingival thickness			t keratinized tissue that needs ortho tx.
Ngan et al. (1991)[35]	Retro-spective/ Post-ortho treatment	NA	T (10): ortho retrusion + autogenous gingival graft prior to the ortho tx C (10): ortho retrusion + no graft	Labial recession	Gingiva biotype change C: 5 no change, 3 thinner, 2 thicker T: 5 no change, 2 thinner, 3 thicker No difference in gingiva index between groups Gingiva recession improved in both group	NA	NA	Similar improvement in both groups. Retrusion of mandibular incisors may override the reduction of recession by pre-ortho autogenous gingival graft.

C= control group; NA= not available; ortho= orthodontic; T= test group; tx= treatment; y/o= year-old

Table 3 Articles excluded with reasons

Article	Reasons for exclusion
Charavet et al., 2017	Case series with n=23
Wu et al., 2015	No reporting of relevant parameters
Wang et al., 2014	Case series with n=8
Coscia et al., 2013	Case series with n=14
Ahn et al, 2012	Case series with n=15
Fergusson et al., 2005	Review article
Kim et al., 2011	Case report with n=2
Nowzari et al., 2008	Case report with n=1
Batista et al., 2014	Case report with n=1
Wilcko et al., 2005	Case report with n=3
Yezdani, 2012	Case report with n=2
Wilcko et al., 2001	Case report with n=2

Table 4 Risk of Bias Assessment of Included randomized controlled trials

Criteria (Higgins and Green, 2011)[23]	**Shoreibah et al. (2012)[25]**	**Bahamman et al. (2016)[26]**
Random sequence generation (selection bias)	Low risk	Low risk
Allocation concealment (selection bias)	Low risk	Low risk
Blinding of participants and personnel (performance bias)	High risk	High risk
Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Unclear risk	Low risk
Incomplete outcome data addressed (attrition bias)	High risk	High risk
Selective reporting (reporting bias)	Low risk	Low risk
Other bias	Unclear risk	Unclear risk

Comments	Reported data showed discrepancy between results and table	Reported data showed discrepancy between abstract and results

Table 5 Newcastle-Ottawa Quality Assessment Scale of Included Case Control Studies and Cohort Studies[24]

	Study type	Selection (max: ★★★★)	Comparability (max: ★★)	Outcome (max: ★★★)
Brugnami et al. (2017)[27]	Cohort study	★★★	★★	★★
Makki et al. (2015)[28]	Cohort study	★	★	★
Wilcko et al. (2015)[29]	Case Control	★★	★	★
Ahn et al. (2016)[30]	Cohort study	★★★	★★	★★★
Maynard and Ochsenbein (1975)[12]	Cohort study	★	★	★
Nagan et al. (1991)[35]	Cohort study	★	★	★