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Periodontal health status, oral microbiome, white-spot lesions and oral health related to quality of life-clear aligners versus fixed appliances: A systematic review, meta-analysis and meta-regression

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Objective: Assess and evaluate the different indicators of oral health-related quality of life (OHRQoL) among patients treated with clear aligners (CAs) versus those treated with conventional fixed orthodontics (FAs). **Methods:** An electronic search was performed on the database is Web of Science, Scopus, and Embase databases. Randomized and non-randomized control trials, cross-sectional, prospective cohort and retrospective trials were included. Quality was assessed with risk of bias tool and risk of bias in non-randomised studies. Meta-analyses were performed with random effects models, estimating the standardized and non-standardized mean differences, odds ratio and risk ratio as the measure of effect. The effect on time was determined using a meta-regression model. **Results:** Thirty one articles were included in the qualitative synthesis and 17 in the meta-analysis. CAs had a significantly lower negative impact on QoL, with an "important" effect size, while the influence of time was not significant. Periodontal indicators plaque index (PI), gingival index (GI), probing depth (PD), and bleeding on probing show significantly better values in patients treated with CAs, with moderate to large effect sizes. PI and GI have a significant tendency to improve over time. In microbiological indicators, CAs present a lower biofilm mass without differences in the percentage of patients with high counts of *Streptococcus mutans* and *Lactobacilli* bacteria. The risk of white spot lesion onset is ten times lower in carriers of CAs. **Conclusions:** Patients wearing CAs show better periodontal indicators, less risk of white spot development, less biofilm mass and a better QoL than patients with FAs.

Key words: Removable, Tooth movement, Orthodontic treatment

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INTRODUCTION

Due to the growing demand for aesthetic treatments, clear aligners (CAs) are one of the patients' preferred treatment options.[1] The number of patients receiving this type of treatment has significantly increased over the past decade, and this tendency is expected to continue in the future.[2]

Manufacturers market CAs as a treatment that provides a better patient experience than conventional brackets in terms of discomfort, treatment duration, aesthetics, and quality of life (QoL).[3,4] According to some authors, CAs treatment is associated with increased comfort and lower analgesic consumption,[5,6] shorter chair time and fewer emergency visits compared to conventional braces treatment.[7,8] The clinical performance of the current CA systems seem comparable to that of fixed orthodontics (FAs) in treating most malocclusions.[9]

Fixed appliances have been reported to affect oral hygiene, favoring plaque retention.[7] CAs, being removable, could allow better oral hygiene and could be related to better periodontal conditions.[10,11] Recent evidence from systematic reviews suggests that patients in treatment with CAs show better periodontal health indicators than those wearing traditional braces.[11-13] However, the level of evidence of the articles included in the qualitative or quantitative synthesis was low due to the risk of bias and heterogeneity in the selected studies.[11]

White spot lesions (WSLs) are a major concern when dealing with orthodontic patients. However, their prevalence in patients wearing CAs has been the object of a few reports, and only one systematic review reported on this topic;[14] however, no meta-regression was performed.

Orthodontic appliances can promote plaque retention and a change in the composition of the oral microbiota, with possible effects on periodontal health and risk of caries. Some authors reported a different microbiota composition in plaque or saliva in aligner patients compared to patients wearing FAs.[15,16]

All these findings suggest that aligner treatment tends to have a lower impact on oral health and QoL. Few systematic reviews reported on this topic; only one addressed the impact on QoL, but no meta-analysis was performed.[17] This systematic review aimed to perform a quantitative assessment of the oral health indicators and QoL in patients treated with CAs compared to patients wearing classic braces.

The aim of this systematic review can be resumed by the following PICO question: (P) in orthodontic patients (I) treated with CAs (C) or conventional fixed appliances (O) is there a difference in variables related to periodontal health such as gingival index (GI), plaque index (PI), probing depth (PD), bleeding on probing (BOP), WSLs, bacterial count in saliva or plaque and their impact on oral health-related QoL (OHRQoL)? The Null Hypothesis was that no correlation exists between these indicators and the modality of orthodontic treatment.

MATERIALS AND METHODS

This systematic review and meta-analysis was conducted according to the statement of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[18] The review protocol was registered in PROSPERO (registration number CRD42022314530; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=314530).

Eligibility criteria

The inclusion and exclusion criteria were developed in accordance with the previously reported PICO question.

The included studies were as follows: controlled clinical trials; randomized clinical trials (RCTs); cohort studies and observational studies, both retrospective and prospective; published or in press; published in English; comparing the variables included in the PICO questions in patients treated with CAs or traditional fixed appliances.

Exclusion criteria: clinical studies not comparing the 2 treatment modalities.

Information sources

An electronic search was performed on the following databases: Web of Science (including Core Collection, Medline, KCI Korean Journal Database, and Scielo Citation Index), Scopus, Embase, Opengrey, and Google Scholar. The search was conducted on December 31, 2021. The search was not restricted in time. A manual search of additional articles related to the topic was carried out on the references of the selected articles.

Search strategy

The search was performed with a combination of keywords and the corresponding Boolean operators, as reported in Table 1.

Study selection

Two authors (A.S.L. and J.M.M.) performed the search process following the guidelines established in PRISMA Protocol.[18] The authors were calibrated first and presented a high inter-operator reliability (kappa = 0.87). The retrieved articles were first selected by titles and abstracts, selecting any potentially eligible studies. Subsequently, the same researchers performed a second screening of the full text of the articles according to the defined inclusion and exclusion criteria. A third reviewer (M.A.) was consulted in case of any disagreement.

Table 1. The search strings inserted in the search tools of Scopus, Embase and Web of Science. The number of retrieved items (N) is presented

Database	Search string	N
Scopus	TITLE-ABS-KEY ("Clear aligners" OR "Invisalign" OR "aligners") AND TITLE-ABS-KEY ("Fixed Orthodontic Appliances" OR "fixed appliances" OR "brackets") AND TITLE-ABS-KEY ("plaque index" OR "periodontal health" OR "oral health" OR "periodontal disease" OR "periodontitis" OR "gingivitis" OR "periodontal bacteria" OR "microbiota" OR "biofilm" OR "white spot lesions" OR "enamel demineralization" OR "cariogenic bacteria" OR "quality of life" OR "oral health related quality of life")	65
Embase	('plaque index'/exp OR 'plaque index' OR 'periodontal health'/exp OR 'periodontal health' OR 'oral health'/exp OR 'oral health' OR 'periodontal disease'/exp OR 'periodontal disease' OR 'periodontal bacteria' OR 'periodontitis'/exp OR 'periodontitis' OR 'gingivitis'/exp OR 'gingivitis' OR 'microbiota'/exp OR 'microbiota' OR 'biofilm'/exp OR 'biofilm' OR 'white spot lesions' OR 'enamel demineralization' OR 'cariogenic bacteria' OR 'quality of life'/exp OR 'quality of life' OR 'oral health related quality of life'/exp OR 'oral health related quality of life') AND ('fixed orthodontic appliances'/exp OR 'fixed orthodontic appliances' OR 'brackets' OR 'fixed appliances' OR 'orthodontic'/exp OR 'orthodontic') AND ('clear aligners' OR 'invisalign'/exp OR 'invisalign' OR 'aligners') AND ('article'/it OR 'article in press'/it) AND 'human'/de	183
Web of Science	((AB=("Clear aligners" OR "Invisalign" OR "aligners")) AND AB=("Fixed Orthodontic Appliances" OR "fixed appliances" OR "brackets")) AND (AB=("plaque index" OR "periodontal health" OR "oral health" OR "periodontal disease" OR "periodontitis" OR "gingivitis" OR "periodontal bacteria" OR "microbiota" OR "biofilm" OR "white spot lesions" OR "enamel demineralization" OR "cariogenic bacteria" OR "quality of life" OR "oral health related quality of life"))	33

Data collection process

Data from the selected articles were extracted by one reviewer and exported to an Excel datasheet (Microsoft Office for Mac 2011 package; Microsoft, Redmond, WA, USA) organized according to the Cochrane Consumers and Communication Review Group data extraction template. A second reviewer checked the extracted data, and disagreements were resolved by consensus. No author was contacted in this phase since all numerical data were provided in the published papers.

Data items

The following data were extracted: a) name of the authors; b) year of publication; c) study type; d) sample size of the group treated with FAs; e) sample size of the group treated with CAs; f) sex of the participants; g) mean age, and standard deviation; h) treatment/observation time; i) outcome variables analyzed; and j) conclusions. Unless the same data were gathered from at least 2 selected studies, the relevant data could only be described but not synthesized. The following outcome variables for OHRQoL assessment were considered: World Health Organization Quality of Life (WHOQOL)-BREF, Oral Health Impact Profile (OHIP)-14 and OHIP-SF19, and for periodontal health assessment: PI, BOP, GI, and periodontal probing depth. Biofilm mass, *Streptococcus mutans* (*S. mutans*), and *Lactobacillus* counts were considered for oral microbiome assessment. The percentage of patients who developed WSLs was the variable observed for non-cavitated caries lesions. No new data was generated or analyzed in support of this research.

Quality assessment

The quality assessment of the included studies was performed independently by 2 reviewers (A.S.L., J.M.M.), and if necessary, any disagreement was discussed and resolved by consensus. The quality assessment for RCTs was performed using the Cochrane Risk of Bias 1 tool (RoB-1).[19]

The tool assesses the following items: 1) random sequence generation, 2) allocation concealment; 3) blinding of participants and personnel; 4) blinding of outcome assessment; 5) incomplete outcome data; 6) selective reporting bias; and 7) other bias. Every single item can be considered as having a low risk, unclear, high risk or no information.

The Cochrane Risk Of Bias in Non-randomised Studies of Interventions (ROBINS-I) tool was used to assess non-randomized studies of interventions and observational studies.[20]

The tool assesses the following items: 1) bias due to confounding; 2) bias in selection of participants into the study; 3) bias in classification of interventions; 4) bias due to deviations from intended interventions; 5) bias due to missing data; 6) bias in measurement of the outcome; and 7) bias in selection of the reported result.

Table 2. The key characteristics of the included studies

Author	Country	Study type	Age (yr)	Assesment timing	No. of patients/ sex	Outcome variables
Abbate et al.[23] (2015)	Italy	RCT	CAs: 10–18 FAs: 10–18	- Beginning of treatment - 3, 6, 12 mo	CAs: 22/N/A FAs: 25/N/A	Plaque score (PS), bleeding score (BS), PD, PI, BOP Periodontal pathogens and microbial biofilm mass through real time PCR (*A. Actinomycetemcomitans*; *P. gingivalis*; *P. intermedia*; *T. Forsythia*)
Alajmi et al.[48] (2020)	Kuwait	RS	CAs: 32.9 ± 6.9 FAs: 23.6 ± 5.3	N/A	CAs: 20 F/10 M FAs: 21 F/9 M	Score of a OHRQoL questionnaire
Albhaisi et al.[24] (2020)	Jordan	RCT	CAs: 21.2 FAs: 21.3	- Beginning of treatment - 3 mo	CAs: 20 F/7 M FAs: 19 F/3 M	Fluorescence loss (DF), number of newly developed lesions, deepest point in the lesion (DFMax), lesion area (pixels), and plaque surface area (DR30)
AlSeraidi et al.[32] (2021)	India	PCS	CAs: 27.8 ± 6.9 FAs: 26.4 ± 7.3 LOs: 30.0 ± 6.9	6 to 9 wk	CAs: 21 F/18 M FAs: 22 F/19 M LOs: 20 F/17 M	WHOQOL-BREF questionnaire, physical health, psychological wellbeing, social relationships, environment and overall score
Antonio-Zancajo et al.[33] (2020)	Spain	PCS	CAs: 33.4 ± 5.1 FAs: 24.7 ± 4.1 LOs: 33.8 ± 8.2 SLB: 28.0 ± 9.7	- 4, 8, 24 hr - 2–7 days - 1 mo	CAs: 14 F/16 M FAs: 17 F/13 M LOs: 17 F/13 M SLB: 18 F/12 M	- Modified McGill questionnaire for pain assessment - Oral health impact profile-14 (OHIP-14) questionnaire
Azaripour et al.[49] (2015)	Germany	RS	CAs: 31.9 ± 13.6 FAs: 16.3 ± 6.9	- Before treatment - CAs: 12.6 ± 7.4 mo - FAs: 12.9 ± 7.2 mo	CAs: 39 F/11 M FAs: 34 F/ 16 M	SBI, approximatye plaque index (API), GI Non validated QoL questionnaire
Baseer et al.[44] (2021)	Saudi Arabia	CSS	CAs: 25.0 ± 8.1 FAs: 24.9 ± 8.1	One week after an appliance activation - CAs: 9.56 ± 9.62 mo - FAs: 11.51 ± 10.19 mo	CAs: 29 F/3 M FAs: 99 F/19 M	OHRQoL questionnaire same than Alajmi et al.[49]
Buschang et al.[50] (2019)	USA	RS	CAs: 30.4 ± 14.4 FAs: 29.2 ± 11.5	- Before treatment - CAs: 1.5 ± 0.9 yr - FAs: 2.5 ± 1.3 yr	CAs: 156 F/88 M FAs: 130 F/76 M	- Percent of patients who developed WSLs - OH assessment
Chhibber et al.[25] (2018)	Australia	RCT	CAs: 16.6 ± 4.0 FAs: 14.6 ± 3.9 SLB: 15.4 ± 3.5	- Before treatment - 9, 18 mo	CAs: 7 F/20 M SLB: 13 F/9 M FAs: 10 F/12 M	PI, GI, PBI
Dallel et al.[34] (2020)	Tunisia	PCS	CAs: 16.8 ± 2.0 FAs: 15.2 ± 3.0 AP: 13.2 ± 2.0	- Before treatment - 1, 9 mo	CAs: 17 F/14 M FAs: 22 F/25 M AP: 16 F/18 M	Volume and salivary flow, salivary pH measurement; buffering capacity determination; electrolytes, salivary enzymes, and substrate; Trolox equivalent antioxidant capacity (TEAC), lipid peroxidation, percent of WSLs

Table 2. Continued

Author	Country	Study type	Age (yr)	Assesment timing	No. of patients/ sex	Outcome variables
Flores-Mir et al.[45] (2018)	Canada	CSS	Total: 18–25	- 6 mo	CAs: 81 FAs: 41 89 F/33 M	Dental impacts on daily living (DIDL) questionnaire, patient satisfaction questionnaire (PSQ)
Gao et al.[35] (2021)	China	PCS	CAs: 26.0 ± 5.5 FAs: 24.6 ± 5.2	Pain and anxiety: 1, 3, 5, 7, 14 days QoL: 1, 7, 14 days	CAs: 42 F/13 M FAs: 42 F/13 M	Pain assessment (VAS) State-trait anxiety inventory (STAI) OHIP-14 questionnaire
Gujar et al.[26] (2019)	India	RCT	Total: 12–32 Mean: 28.0 ± 4.0	- Before treatment - 21 days - 9 mo	CAs: 11 F/9 M FAs: 12 F/8 M	PI, GI, BOP, cytokine levels in gingival crevicular fluid
Gujar et al.[36] (2020)	India	PCS	Total: 11–29	- 30 days	CAs: 20 FAs: 20 LOs: 20	Microbial profile using checkerboard DNA-DNA hybridization technique
Han[51] (2015)	China	RS	Total: 35–74 Mean: 53.0 ± 9.4	- Beginning of treatment - End of treatment	CAs: 16 FAs: 19 21 F/14 M	PI, GI, PD, bone level assessed on OPG
Karkhanechi et al.[15] (2013)	USA	PCS	CAs: 28.0 ± 6.9 FAs: 34.0 ± 7.2	- Beginning of treatment - 6 wk - 6, 12 mo	CAs: 12 F/8 M FAs: 16 F/6 M	PI, GI, PPD, BOP
Levrini et al.[27] (2013)	Italy	RCT	CAs: 24.6 ± 6.4 FAs: 25.7 ± 3.4 CG: 25.0 ± 3.4	- Beginning of treatment - 1, 3 mo	CAs: 7 F/3M FAs: 7 F/3M CG: 7 F/3M	PI, BOP, PD, periodontal pathogens and microbial biofilm mass through real time PCR
Levrini et al.[28] (2015)	Italy	RCT	Total: 16–30 Mean: 2.3	- Beginning of treatment - 1, 3 mo	CAs: 27 F/5 M FAs: 17 F/18 M CG: 8 F/2 M	PI, BOP, PD, periodontal pathogens and microbial biofilm mass through real time PCR
Lombardo et al.[37] (2021)	Italy	PCS	CAs: 21.0 ± 0.4 FAs: 14.0 ± 0.8	- Beginning of treatment - 1, 3, 6 mo	CAs: 9 F/5 M FAs: 8 F/5 M	Periodontal pathogens and microbial biofilm mass through real time PCR (*A. Actinomycetemcomitans*, *P. Gingivalis*, *F. Nucleatum*, *C. Rectus*, *Tenticola* and *T. Forsythia*)
Madariaga et al.[38] (2020)	Italy	PCS	CAs: 34.7 ± 12.5 FAs: 20.6 ± 8.1	- Beginning of treatment - 3 mo	CAs: 20 FAs: 20 26 F/14 M	PI, BOP, PD, REC
Miethke and Vogt[29] (2005)	Germany	NRCT	Total: 18–51 Mean: 30.1	3 assessments at 3–4 wk interval starting at least after 6 mo into treatment	CAs: 30 FAs: 30 43 F/17 M	PI, GI, PD, PBI
Miller et al.[39] (2007)	USA	PCS	CAs: 38.0 ± 12.4 FAs: 28.6 ± 8.7	- Beginning of treatment - 1–7 days	CAs: 22 F/11M FAs: 6 F/21 M	Pain (VAS), QoL evaluated with the geriatric oral health assessment index; pain medication intake
Mulla Issa et al.[46] (2020)	China	CSS	CAs: 26.9 ± 4.8 FAs: 26.7 ± 5.2 CFAs: 27.7 ± 8.2 SLB: 26.9 ± 5.2	N/A, at least 6 mo	CAs: 12 F/8 M FAs: 7 F/13 M CFAs: 11 F/9 M SLB: 10 F/10 M	PI, GI, GBI, SBI, PBI, BOP, BPE

Table 2. Continued

Author	Country	Study type	Age (yr)	Assesment timing	No. of patients/ sex	Outcome variables
Mummolo et al.[40] (2020)	Italy	PCS	CAs: 21.5 ± 1.5 FAs: 23.3 ± 1.6 RP: 18.2 ± 1.5	- Beginning of treatment - 3, 6 mo	CAs: 12 F/18 M FAs: 12 F/22 M RP: 10 F/16 M	PI, salivary flow and saliva buffering power through CRT® Buffer system; bacterial count (*S. mutans* and *Lactobacillus*) through CRT® bacteria
Mummolo et al.[41] (2020)	Italy	PCS	CAs: 20.4 ± 1.7 FAs: 21.3 ± 1.7	- Beginning of treatment - 3, 6 mo	CAs: 16 F/24 M FAs: 18 F/22 M	PI, salivary flow and saliva buffering power through CRT® Buffer system; bacterial count (*S. mutans* and *Lactobacillus*) through CRT® bacteria
Shalish et al.[30] (2012)	Israel	NRCT	Total: 18–60	- 1, 2 wk	CAs: 21 FAs: 28 LOs: 19 45 F/23 M	Score of a OHRQoL questionnaire
Sharma et al.[47] (2021)	Canada	CCS	Total: 11–18 Mean: 14.9 ± 1.9	- 6 mo	CAs: 37 FAs: 37 44 F/30 M	Child oral health impact profile-short form 19 (COHIP-SF 19)
Sifakakis et al.[16] (2018)	Greece	PCS	CAs: 13.9 ± 2.0 SLB: 13.6 ± 1.5	- Beginning of treatment - 2 wk - 1 mo	CAs: 8 F/7M SLB: 9 F/6 M	s-PII, s-GI, salivary counts of *S. mutans*, *L. acidophilus*, *S. sanguinis*
Srinath et al.[42] (2016)	India	PCS	CAs: 35.0 ± 6.9 FAs: 34.0 ± 7.2	- 6 wk - 6, 12 mo	CAs: 12 F/8 M FAs: 18F/8 M	GI, PI, BOP, PD
Wang et al.[43] (2019)	China	PCS	Total: 20–25	- 6 mo	CAs: 7 FAs: 12 CG: 7	High-throughput pyrosequencing was performed based on the 16S rRNA gene, Shannon index
Zamora-Martínez et al.[31] (2021)	Spain	NRCT	Total: 18–68 Mean: 37.4 ± 14.6	- Beginning of treatment - 6 mo - End of treatment: 19.6 ± 4.7 mo	CAs: 30 FAs: 30 CFAs: 30 LOs: 30 59 F/61 M	OHIP-14 questionnaire

Values are presented as range or mean ± standard deviation.
RCT, randomized clinical trial; CAs, clear aligners; FAs, conventional fixed appliances; N/A, not available; PD, probing depth; PI, plaque index; BOP, bleeding on probing; PCR, polymerase chain reaction; RS, retrospective study; F, females; M, males; OHRQoL, oral health related quality of life; DF, fluorescence loss; DFMax, deepest point in the lesion; DR30, plaque surface area; PCS, prospective/cohort study; LOs, lingual orthodontics; SLB, self-ligating brackets; SBI, sulcus bleeding index; GI, gingival index; CSS, cross-sectional study; WSLs, white spots lesions; OH, oral higiene; PBI, papilla bleeding index; AP, appliance; VAS, visual analogic scale; OPG, orthopantomography; PPD, pocket probing depth; CG, group control; REC, gingival recessions; NRCT, non randomizad clinical trial; CFAs, aesthetic brackets; GBI, gingival bleeding index; BPE, basic periodontal exam index; RP, removable positioner; s-PII, simplified plaque index; s-GI, simpified gingival index.

Every single item can have a low, moderate, serious or critical risk of bias.

Statistical analysis

Data were combined through a random effect model (inverse variance method) for quantitative synthesis. To combine data from studies conducted with different measurement scales, the standardized mean difference was used as a measure of effect size. According to Cohen interpretation, a d = 0.2 was considered as a 'small' effect size, 0.5 as a 'medium' effect size and greater than 0.8 as a 'large' effect size. Other effect sizes used were no standardized mean difference, odds ratio (OR) and relative risk.

The level of significance was set at $P < 0.05$ for the Z test, and the Cochrane Q test and the I^2 were employed to quantify the heterogeneity between studies. The heterogeneity was considered high if the Q test presented a P value < 0.1 and I^2 was > 75%. A meta-regression was performed to assess the influence of time on the effect size. Forest plots were constructed to visually represent the meta-analysis. Publication bias was estimated using Duval and Tweedie's trim and fill, which aims at estimating potentially missing studies to gather the funnel plot's symmetry and compares the change in effect estimate.[21] Moreover, the classic fail-safe number was calculated to quantify the number of missing non-significant studies that should be added to make the combined effect size statistically insignificant. Finally, the Egger equation intercept deviation to 0 was observed, as well as statistical significance.[22] Meta-analysis and meta-regression were performed using Comprehensive Meta-Analysis Software V3.0 (Biostat Inc., Englewood, NJ, US).

RESULTS

The electronic and manual search allowed us to identify 285 published items; after removing duplicates, 207 records were screened using their title and abstracts. After this first screening, 33 studies were assessed for eligibility by screening the full text. After applying the inclusion and exclusion criteria, 2 studies were removed, and the remaining papers were included in the qualitative synthesis. The key features of the included studies are shown in Table 2. The studies were published between 2005 and 2021. A total of 31 records were included in the qualitative synthesis: 6 studies were RCTs,[23-28] 3 non-randomized clinical trials (non-RCTs),[29-31] 14 prospective or cohort studies,[15,16,32-43] 4 cross-sectional studies,[44-47] 4 retrospective studies.[48-51] The flowchart of the screening process according to the PRISMA statement is displayed in Figure 1. Finally, 17 studies were included in the quantitative synthesis.

Effect on oral health-related quality of life

To explore the effect of CAs versus FAs on OHRQoL

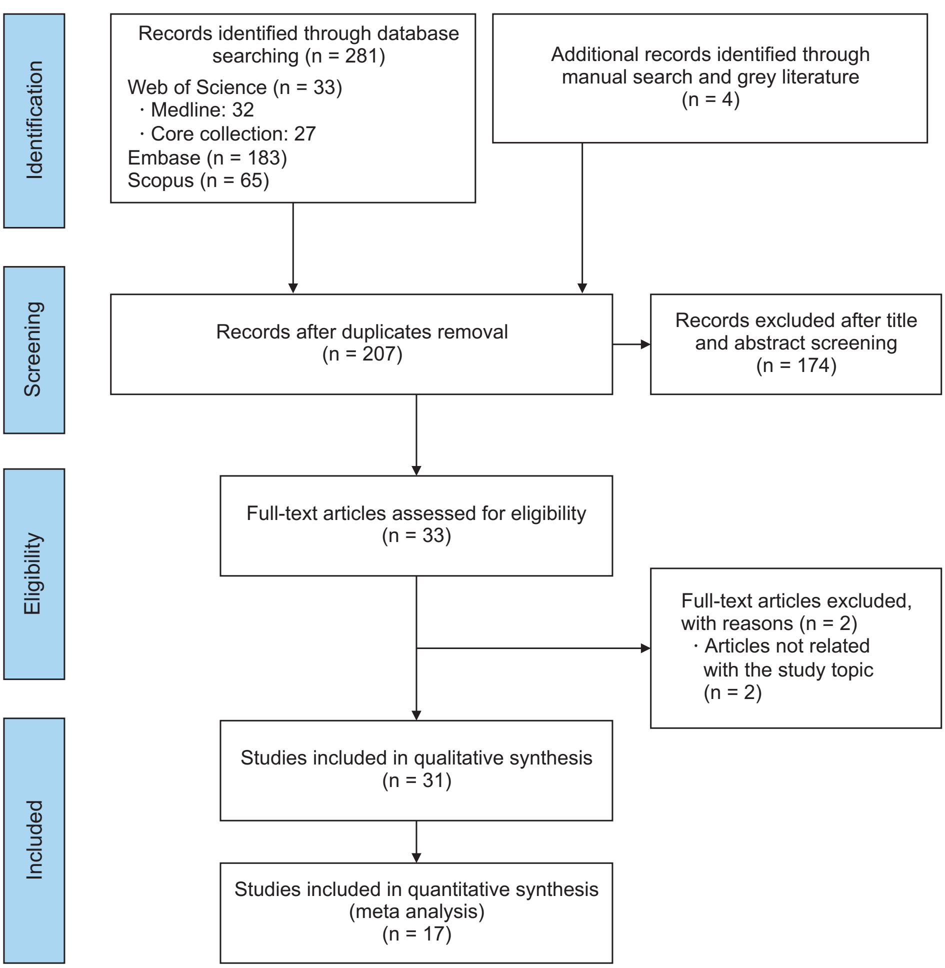

Figure 1. Flow diagram.

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between the first week and the first 6 months of treatment, 4 studies were selected,[32,33,44,47] and the overall questionnaire scores were combined. A Mantel-Haenszel method for random effects was employed. The heterogeneity could be considered high Q = 95.3; $P < 0.001$ and an $I^2 = 96.8\%$. The standard difference in means was −1.57 (95% confidence interval [CI], −3.04 to −0.10; $P = 0.037$), indicating a lower and better impact of CAs

Study name	Std diff in means	Lower limit	Upper limit	Z value	*P* value	Clear aligners	Conventional
Alseraidi 2021	-4.846	-5.715	-3.976	-10.923	< 0.001	39	41
Antonio-Zancajo 2020	-1.049	-1.588	-0.509	-3.808	< 0.001	30	30
Baseer 2021	-0.273	-0.665	0.119	-1.367	0.172	32	118
Sharma 2021	-0.306	-0.765	0.152	-1.309	0.190	37	37
	-1.568	-3.039	-0.098	-2.090	0.037		

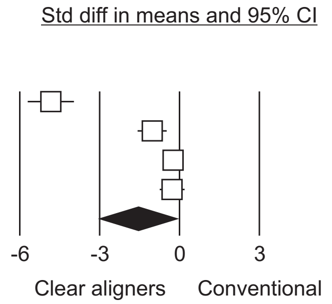
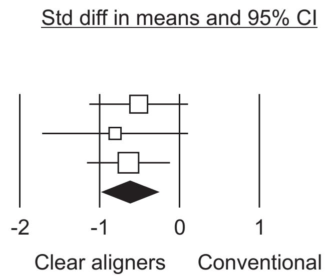


Figure 2. Oral health-related quality of life meta-analysis and Forest plot.
Std diff, standard difference; CI, confidence interval.

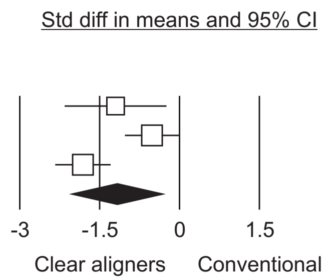
At 1 month

Study name	Std diff in means	Lower limit	Upper limit	Z value	*P* value	Clear aligners	Conventional
Karkhanechi 2013	-0.506	-1.121	0.109	-1.613	0.107	22	20
Levrini 2015	-0.804	-1.715	0.107	-1.729	0.084	10	10
Miethke 2005	-0.637	-1.156	-0.118	-2.407	0.016	30	30
	-0.618	-0.982	-0.254	-3.331	0.001		



At 3 months

Study name	Std diff in means	Lower limit	Upper limit	Z value	*P* value	Clear aligners	Conventional
Levrini 2015	-1.188	-2.139	-0.237	-2.449	0.014	10	10
Miethke 2005	-0.503	-1.017	0.011	-1.916	0.055	30	30
Mummolo 2020	-1.800	-2.319	-1.280	-6.791	< 0.001	40	40
	-1.161	-2.054	-0.268	-2.547	0.011		



At 6–12 months

Study name	Std diff in means	Lower limit	Upper limit	Z value	*P* value	Clear aligners	Conventional
Abbate 2015	-5.968	-7.303	-4.632	-8.758	< 0.001	22	25
Azaripour 2015	-0.425	-0.821	-0.029	-2.102	0.036	50	50
Han 2015	0.061	-0.604	0.726	0.179	0.858	16	19
Mulla Issa 2020	-5.306	-6.623	-3.988	-7.893	< 0.001	20	20
Mummolo 2020	-3.960	-4.714	-3.206	-10.293	< 0.001	40	40
	-3.055	-5.206	-0.904	-2.784	0.005		

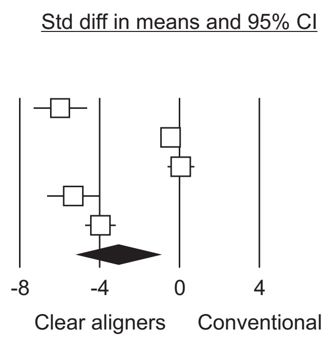


Figure 3. Plaque index at 1, 3, and 6–12 months into treatment meta-analysis and Forest plot.
Std diff, standard difference; CI, confidence interval.

on the overall QoL (Figure 2). According to the Cohen classification, the effect size could be considered "large".

A meta-regression was carried out with a random effect model to explore the effect of time on the OHRQoL. The variable time did not appear to significantly affect the model (Q = 0.04; *P* = 0.846).

Effect on plaque index

The differences in plaque index were analyzed at 1 and 3 months into treatment and between 6 and 12 months into treatment. To estimate the difference of standardized means at 1 month into treatment, 3 studies[15,28,29] were combined through a fixed effect model since no heterogeneity was detected (Q = 0.292; *P* = 0.864; I^2 = 0%). A statistically significant difference of −0.62 (95% CI, −0.98 to −0.25; *P* = 0.001) was obtained, indicating how CA patients display a lower plaque index than the ones in FAs 1 month into treatment. According to Cohen's classification, the size of the effect could be considered "medium" (Figure 3).

The study of the effect at 3 months into treatment in 3 studies[28,29,41] were combined through a random effect

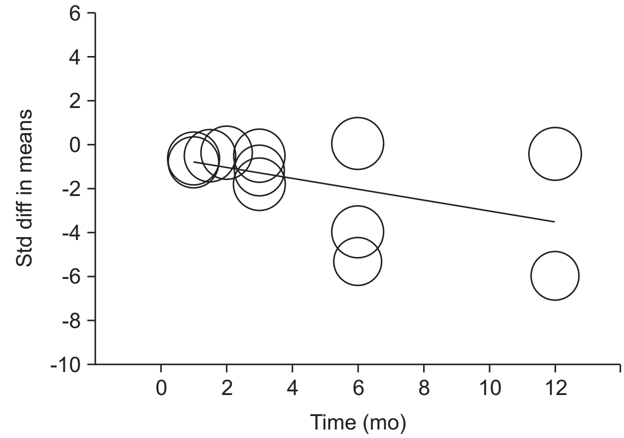
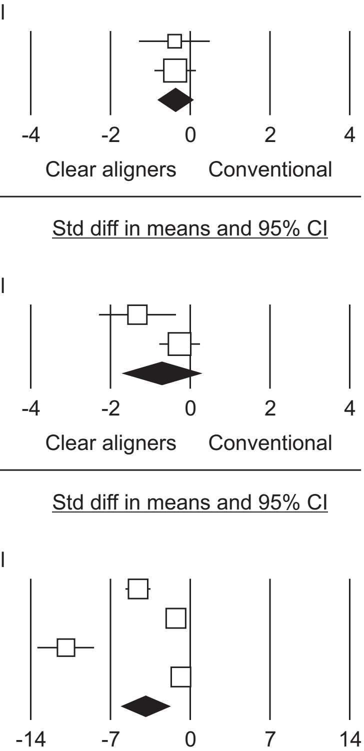


Figure 4. Meta-regression scatter plot of plaque index standardized difference in mean at different time points (months).
Std diff, standard difference.



At 1 month

Study name	Std diff in means	Lower limit	Upper limit	Z value	*P* value	Clear aligners	Conventional
Levrini 2015	-0.400	-1.285	0.485	-0.886	0.376	10	10
Miethke 2005	-0.383	-0.894	0.128	-1.470	0.142	30	30
	-0.387	-0.830	0.055	-1.716	0.086		

At 3 months

Study name	Std diff in means	Lower limit	Upper limit	Z value	*P* value	Clear aligners	Conventional
Levrini 2015	-1.314	-2.280	-0.347	-2.664	0.008	10	10
Miethke 2005	-0.264	-0.772	0.245	-1.017	0.309	30	30
	-0.705	-1.721	0.311	-1.360	0.174		

At 6–12 months

Study name	Std diff in means	Lower limit	Upper limit	Z value	*P* value	Clear aligners	Conventional
Abbate 2015	-4.606	-5.699	-3.512	-8.257	< 0.001	25	22
Azaripour 2015	-1.245	-1.673	-0.816	-5.696	< 0.001	50	50
Mulla Issa 2020	-10.932	-13.407	-8.458	-8.659	< 0.001	20	20
Chhibber 2018	-0.836	-1.423	-0.249	-2.793	0.005	27	22
	-3.960	-6.138	-1.783	-3.565	< 0.001		

Figure 5. Gingival bleeding at 1, 3, and 6–12 months into treatment meta-analysis and Forest plot.
Std diff, standard difference; CI, confidence interval.

model due to the high heterogeneity of the meta-analyses (Q = 12.1; P = 0.002; I^2 = 83.4%). A statistically significant difference in standardized means of −1.16 (95% CI, −2.05 to −0.27; P = 0.011) was detected. CA patients display a lower plaque index than the ones in FAs at 3 months into treatment. According to Cohen's classification, the effect size could be considered "large" (Figure 3).

At 6–12 months into treatment[23,41,46,49,51] the tendency was maintained with a statistically significant difference of −3.05 between the 2 groups (95% CI, −5.20 to −0.90; P = 0.005), a random effect model was applied due to the high heterogeneity (Q = 164.7; P < 0.001; I^2 = 97.5%), the effect size could be considered "large" (Figure 3).

The values extracted by 8 studies[15,23,28,29,41,46,49,51] were combined through a random effect meta-regression model to explore the influence of time on PI. A statistically significant standardized difference in means of −0.25 (95% CI, 0.48 to −0.02; P = 0.035) was detected for each month into treatment favorable to the CAs group. The effect size is time-dependent and can be considered "medium" at 1 to 3 months into treatment and large 3 to 12 months into treatment (Figure 4).

Effect on gingival bleeding

The differences in gingival bleeding index were analysed at 1 and 3 months into treatment and between 6 and 12 months into treatment. To estimate the difference of standardized means at 1 month into treatment, 2 studies[28,29] were combined through a fixed effect model, since no heterogeneity was detected (Q = 0.001; P = 0.974; I^2 = 0%). A difference of −0.39 (95% CI, −0.83 to −0.06; P = 0.086) was obtained, indicating how CAs patients display lower gingival bleeding than the ones in FAs at 1 month into treatment, although the difference was non-significant (Figure 5).

To explore the effect at 3 months into treatment, 2 studies[28,29] were combined through a random effect model (Q = 3.552; P = 0.0522; I^2 = 71.9%). A difference was detected in standardized means of −0.71 (95% CI, −1.72 to −0.31; P = 0.174). Clear aligner patients at 3 months into treatment display a lower gingival bleeding score than the ones in FAs, but according to what was detected at 1 month, the difference was not statistically significant (Figure 5).

To assess gingival bleeding at 6 to 12 months into treatment, the data from 4 studies[23,25,46,49] were combined through a random model due to the high heterogeneity (Q = 92.8; P < 0.001; I^2 = 96.8%). A statistically significant difference of −3.96 between standardized means was obtained (95% CI, −6.13 to −1.78; P < 0.001). The effect size could be considered "large" (Figure 5).

The values extracted from 6 studies[23,25,28,29,46,49] were combined through a random effect meta-regression model to explore the influence of time on Gingival bleeding. A statistically significant standardized difference in means of −0.22 (95% CI, −0.42 to −0.01; P = 0.031) was detected for each month of treatment in CAs patients. The meta-regression model indicates how gingival bleeding decreases with time in CA patients (Figure 6).

Effect on gingival index

The effect on gingival index could not be quantitatively synthesized at 1 and 3 months into treatment because only 1 study reported the full data set was available. However, the studies were included in the meta-regression model.

At 6 to 12 months into treatment, the results of 4 studies[25,46,49,51] were combined through a random model meta-analysis due to the high heterogeneity (Q = 21.44; P < 0.001; I^2 = 86%).

A statistically significant difference of −1.18 between standardized means was obtained (95% CI, −1.99 to −0.36; P < 0.001). The effect size could be considered "large" (Figure 7).

The meta-regression model used to detect the influence of time on the outcome included the data from 5 studies[25,29,46,49,51] gathered at 7 different time points. The effect of time on the gingival index was insignificant (Q = 0.25; P = 0.616), as the standardized difference means −0.02 (95% CI, −0.09 to 0.06) for each month into treatment.

Effect on probing depth

The effect on probing depth was explored at 1 and 3 months into treatment. The data between 6 and 12

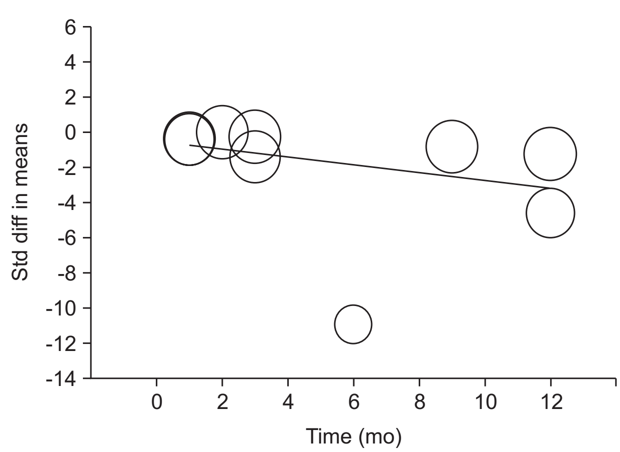


Figure 6. Meta-regression scatter plot of gingival bleeding index standardized difference in mean at different time points (months).
Std diff, standard difference.

Study name	Std diff in means	Lower limit	Upper limit	Z value	*P* value	Clear aligners	Conventional
	Statistics for each study					Sample size	
Azaripour 2015	-0.444	-0.841	-0.048	-2.195	0.028	50	50
Han 2015	-0.811	-1.502	-0.119	-2.297	0.022	16	19
Chhibber 2018	-1.034	-1.633	-0.435	-3.384	0.001	27	22
Mulla Issa 2020	-2.637	-3.485	-1.790	-6.100	< 0.001	20	20
	-1.175	-1.987	-0.364	-2.840	0.005		

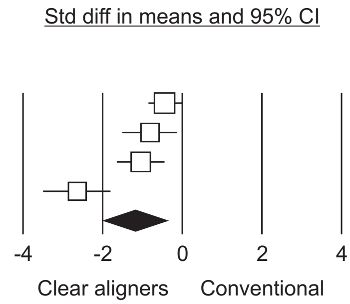
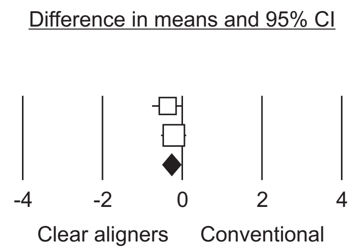


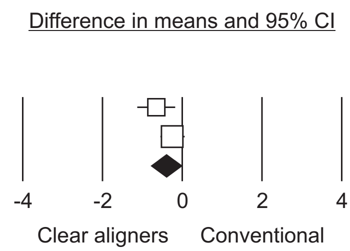
Figure 7. Gingival index 6–12 months into treatment meta-analysis and Forest plot.
Std diff, standard difference; CI, confidence interval.

Study name	Difference in means	Lower limit	Upper limit	Z value	*P* value	Clear aligners	Conventional
	Statistics for each study					Sample size	
Levrini 2015	-0.350	-0.737	0.037	-1.773	0.076	10	10
Miethke 2005	-0.210	-0.523	0.103	-1.315	0.188	30	30
	-0.265	-0.509	-0.022	-2.137	0.033		



At 1 month

Study name	Difference in means	Lower limit	Upper limit	Z value	*P* value	Clear aligners	Conventional
	Statistics for each study					Sample size	
Levrini 2015	-0.650	-1.122	-0.178	-2.697	0.007	10	10
Miethke 2005	-0.240	-0.535	0.055	-1.595	0.111	30	30
	-0.402	-0.795	-0.009	-2.005	0.045		



At 3 months

Figure 8. Probing depth at 1 and 3 months into treatment meta-analysis and Forest plot.
CI, confidence interval.

months could not be quantitatively assessed since only 1 study reporting the full data set was available. However, the study could be included in the meta-regression model. At 1 month[28,29] into treatment, the difference in means between the 2 groups was statistically significant and equal to –0.26 (95% CI, –0.51 to –0.02 mm; P = 0.030). Due to the low heterogeneity, a fixed model was used (Q = 0.304; P = 0.581; I^2 = 0%).

The data from 2 studies[28,29] were analyzed through a random effect model due to the heterogeneity magnitude (Q = 2.082; P = 0.149; I^2 = 51.9%) to study the effect at 3 months into treatment. The difference in means between the 2 treatment groups was equal to –0.04 mm and statistically significant (95% CI, –0.80 to –0.01; P = 0.045) (Figure 8).

The meta-regression model applied to detect the influence of time on the outcome included the data from 3 studies[28,29,51] gathered at 4 different time points. The effect of time on probing depth was not significant (Q = 0.25; P = 0.113).

Effect on biofilm mass

To estimate the differences in biofilm mass 1 month into treatment the data proceeding from 2 studies[16,28] could be quantitatively synthetized. The standardized difference in means was statistically significant and equal to –0.60 (95% CI, –1.17 to –0.03; P = 0.04). Due to the low heterogeneity a fixed effect model was applied test (Q = 1.09; P = 0.296; I^2 = 8.3%) (Figure 9).

To quantify the effect of time on the outcome in CAs and FA patients, a meta-regression model was applied to the data provided by 2 studies at 3 different time points. The effect of time on biofilm mass was not significant (Q = 0.57; P = 0.448).

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Study name	Std diff in means	Lower limit	Upper limit	Z value	*P* value	Clear aligners	Conventional
	Statistics for each study					Sample size	
Levrini 2015	-0.988	-1.916	-0.060	-2.086	0.037	10	10
Sifakakis 2018	-0.362	-1.083	0.360	-0.982	0.326	15	15
	-0.597	-1.167	-0.028	-2.055	0.040		

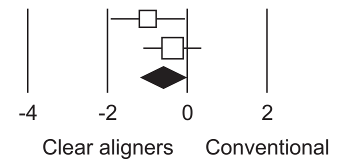

Figure 9. Biofilm mass 1 month into treatment meta-analysis and Forest plot.
Std diff, standard difference; CI, confidence interval.

Study name	Odds ratio	Lower limit	Upper limit	Z value	*P* value	Clear aligners	Conventional
	Statistics for each study					Events/total	
Mummolo 2020	0.132	0.007	2.647	-1.323	0.186	0/40	3/40
Sifakakis 2018	0.286	0.026	3.121	-1.027	0.304	12/15	14/15
	0.212	0.033	1.372	-1.628	0.104		

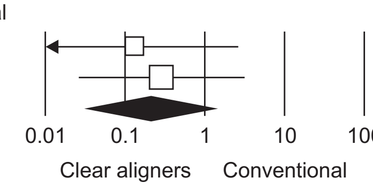

Figure 10. Odds ratio of high concentration of *Streptococcus mutans* between 4 and 12 weeks into treatment, Forest plot and meta-analysis.
CI, confidence interval.

Study name	Odds ratio	Lower limit	Upper limit	Z value	*P* value	Clear aligners	Conventional
	Statistics for each study					Events/total	
Mummolo 2020	0.325	0.013	8.222	-0.682	0.495	0/40	1/40
Sifakakis 2018	0.312	0.012	8.285	-0.696	0.486	0/15	1/15
	0.318	0.032	3.182	-0.974	0.330		

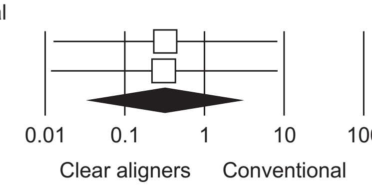

Figure 11. Odds ratio of high concentration of *Lactobacillus* between 4 and 12 weeks into treatment, Forest plot and meta-analysis.
CI, confidence interval.

Effect on *S. mutans* concentration

Two studies[16,41] reported a high concentration of *S. mutans* between 4 and 12 weeks into treatment; the OR was used to quantify the effect size (Figure 10). The meta-analysis was characterized by no heterogeneity (Q = 0.155; *P* = 0.694; I^2 = 0%). An OR of 0.21 could be estimated as non-statistically significant (95% CI, 0.03–1.37; *P* = 0.104).

The data gathered from 2 studies[16,41] at 4 different time points between 2 and 24 weeks into treatment, were analyzed through a meta-regression model. Time did not have a significative effect on high concentration of *S. mutans* (Q = 0.17; *P* = 0.681).

Effect on *Lactobacillus* concentration

As for *S. mutans* concentration, 2 studies[16,41] reporting on the high concentration of *Lactobacillus* between 4 and 12 weeks into treatment were included in the meta-analyses, and the OR was used to quantify the effect size (Figure 11). No heterogeneity characterized the meta-analysis (Q = 0.155; *P* = 0.694; I^2 = 0%). An OR of 0.32 could be estimated as being non-statistically significant (95% CI, 0.03–3.18; *P* = 0.330).

The data gathered from 2 studies[16,41] at 4 different time points between 2 and 24 weeks into treatment, were analyzed through a meta-regression model. The effect of time on the high concentration of *Lactobacillus* was not significant (Q = 0.17; *P* = 0.803).

Effect on the onset of white spot lesions

Two studies[34,50] could be included in the quantitative synthesis; the onset of new WSL was assessed between 9 months into treatment and after treatment. The meta-analysis presented a moderate heterogeneity (Q = 2.652; *P* = 0.103; I^2 = 62.3%).

A Risk Ratio of 0.10 could be estimated (95% CI, 0.02–0.42; *P* = 0.002). The risk of presenting new WSLs in the clear aligner group was 0.1 the risk than the conventional appliances group. The patients in treatment with CAs presented a tenfold lower risk of developing new lesions when compared to the individuals treated with FAs (Figure 12).

Synthesis of results

Table 3 summarizes the estimates and effect sizes of the 14 meta-analyses and 8 meta-regressions for the 9 variables studied.

Publication bias analyses

Publication bias could not be detected by means of Duval and Tweedie's trim and fill methods, no missing studies could be estimated to get a symmetric image that modifies the estimate obtained by the meta-analysis.

Moreover, the number of missing studies that should be added to make the combined effect size statistically insignificant (classic fail-safe number) was very high regarding the plaque index (568), bleeding index (264), and gingival Index (116). The values were lower for probing depth (32) and biofilm mass (5). The number was not estimated for *S. mutans* and *Lactobacillus* concentration. The funnel plots related to OHRQoL, PI, BI and GI display a coincidence between the white diamond that represents the overall effect size calculated in the meta-analysis and the black one that is estimated by the Duval and Tweedie method.

A slight discrepancy could be observed in the case of probing depth and biofilm mass due to 1 study at the right of the standardized mean difference; in both cases, significance was maintained. In the case of *S. mutans* and *Lactobacillus* concentration, the discrepancy, due to one study on the right, was irrelevant since the estimated effect size was insignificant. Funnel plots are available for consultation in Supplementary Figure 1. Publication bias was not estimated regarding WSL since a minimum of 3 studies was required, and only 2 were available.

Quality assessment

The quality assessment performed through the RoB-1 tool on the 6 RCTs included in the qualitative synthesis is displayed in Supplementary Figure 2. The most severe form of bias was the lack of blinding of participants and personnel, which could be observed in all the included studies, followed by the blinding of outcome assessment and the Incomplete outcome data report.

The quality assessment performed through the ROBINSON-1 tool on the 25 non-randomized and observational studies included in the qualitative synthesis is displayed in Supplementary Figure 3.

The most prevalent bias in non-randomized studies was due to confounding, followed by the bias in the selection of participants and the bias in the measurement of the outcome. The risk of bias was low due to deviations from the intended intervention or missing data. At a global level, the risk of bias was regarded as moderate in 32% of the studies and severe in 68%.

DISCUSSION

Patients' aesthetic requirements have favored the use of aligners for orthodontic purposes. Moreover, the patients perceive this treatment as less harmful to their OHRQoL.[2,5] Removable appliances CAs make oral hygiene maintenance easier, facilitating brushing and interdental cleaning. This aspect is paramount and related to

Study name	Statistics for each study: Risk ratio	Lower limit	Upper limit	Z value	*P* value	WSL/total: Clear aligners	Conventional
Buschang 2019	0.048	0.015	0.151	-5.190	< 0.001	3/244	53/206
Dallel 2020	0.217	0.053	0.888	-2.126	0.034	2/31	14/47
	0.096	0.022	0.420	-3.110	0.002		

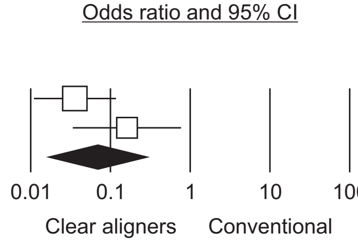

Figure 12. Odds ratio of white spot lesions prevalence at the end of treatment, Forest plot and meta-analysis.
WSL, white spot lesions; CI, confidence interval.

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Table 3. Synthesis of results

Variable	Time point	n	I^2 (%)	Measure of effect	Estimation	*P* value (effect size)	Influence on time
OHRQoL	1 wk to 6 mo	4	96.8	Std diff in means	−1.43 (−3.04 to −0.10)	0.037 (large)	*P* value = 0.685
Plaque index	1 mo	5	0	Std diff in means	−0.62 (−0.98 to −0.25)	0.001* (medium)	*P* value = 0.035*
	3 mo	3	83.4	Std diff in means	−1.61 (−2.05 to −0.27)	0.011* (large)	
	6–12 mo	3	97.5	Std diff in means	−3.05 (−5.20 to −0.90)	0.005* (large)	
Gingival bleeding	1 mo	2	0	Std diff in means	−0.387 (−0.83 to −0.06)	0.086	*P* value = 0.031*
	3 mo	2	71.9	Std diff in means	−0.705 (−1.72 to −0.31)	0.172	
	6–12 mo	4	96.8	Std diff in means	−3.96 (−6.13 to −1.78)	< 0.001* (large)	
Gingival index	6–12 mo	4	86	Std diff in means	−1.18 (−1.99 to −0.36)	0.005* (large)	*P* value = 0.616
Probing depth	1 mo	2	0	Diff in means (mm)	−0.26 mm (−0.51 to −0.02 mm)	0.033*	*P* value = 0.113
	3 mo	2	51.9	Diff in means (mm)	−0.402 mm (−0.80 to −0.01 mm)	0.045*	
Biofilm mass	1 mo	2	8.3	Std diff in means	−0.60 (−1.17 to −0.03)	0.040* (medium)	*P* value = 0.448
S. mutans concentration	4 yr 12 mo	2	0	Odds ratio	0.21 (0.03–1.37)	0.104	*P* value = 0.681
Lactobacillus concentration	4 yr 12 mo	2	0	Odds ratio	0.32 (0.03–3.18)	0.330	*P* value = 0.803
White spot lesions	9 yr 24 mo	2	62.3	Risk ratio	0.10 (0.02–0.42)	0.002* (large)	-

OHRQoL, oral health-related quality of life; Std diff, standard difference; -, not available.
*Statistical significance was set at $P < 0.05$.

periodontal health and dental health throughout treatment. Authors such as Azaripour et al.[49] conclude that CA patients present better periodontal health and report higher satisfaction during orthodontic treatment than patients with FAs.

Within the limitations of the current investigation, we can state that the studies included in our systematic review, meta-analysis and meta-regression suggest that CAs patients display better periodontal health indicators when compared to those in FAs, being our result consistent with the ones reported by Jiang et al.,[11] Rossini et al.,[12] and Lu et al.[52]

In our systematic review, we analyzed 11 studies that assessed OHRQoL between 1 week and 6 months into treatment, of which 4 were included in the meta-analysis. According to our findings, those who underwent CAs treatment reported a lower impact on OHRQoL, with a "significant" effect size, compared to patients treated with FAs. The influence of time on OHRQoL has not been significant. To our knowledge, this is the first systematic review that includes a meta-analysis on the impact of CA treatment on OHRQoL. Zhang et al.[17] performed a systematic review on the same topic but included only 2 articles in the qualitative synthesis and did not perform the quantitative analysis. Their results are inconsistent with ours since they stated that there is little evidence of the improvement of OHRQoL in CA patients compared to FAs ones, highlighting differences only regarding the item "problems during chewing".

At the periodontal level, CA patients presented better indicators than FA patients, with the GI, PI, BI, and PD significantly worse in patients in the FA group. These findings are consistent with what Jiang et al.[11] and Oikonomou et al.[14] previously reported, highlighting significantly lower plaque index scores in CA patients. An integrative review performed by Partouche et al.[13] concluded that CA patients were less subject to plaque accumulation than FA patients. However, among all the indexes evaluated, only PI differed significantly. According to the meta-regression results, the differences between the 2 groups become more noticeable according to the time of treatment and the significant influence

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of time. In terms of plaque index, the effect size turns from “moderate” to “large” 3 months into treatment, maintaining its magnitude at 12 months.

Bleeding on probing displayed a significant difference between the 2 groups 6 months into the treatment, being non-significant earlier into treatment. Our results agree with those presented by Oikonomou et al.,[14] but differ from those of Lu et al.,[52] which highlighted a significantly lower bleeding and plaque index in CA patients at the beginning of treatment from the first to 6 months. Of the 5 articles included by Lu et al.,[52] only 2 met our inclusion criteria.

According to the GI meta-analysis, carried out on 4 studies at 6 and 12 months, a significant difference favorable to CA patients could be observed, while in the meta-regression, where we included 8 measurements from 5 studies, we did not find a significant effect over time.

In the meta-analysis of PD, including 2 studies that assessed this variable at 1 and 3 months, statistically significant differences in favor of CAs could be highlighted, while the meta-regression indicated that the effect was not significantly different over time. These results are consistent with those reported by Rossini et al.,[12] who concluded that periodontal health indices improve significantly during CAs treatment. Jiang et al.[11] and Oikonomou et al.[14] also highlighted how both GI and PD show statistically significantly lower scores in CA patients compared to those wearing FAs. In contrast, authors such as Lu et al.[52] could not retrieve any statistically significant differences between the PD and the GI when the 2 treatment modalities were compared.

Regarding the microbiological parameters analyzed, we could not find any significant differences in the OR for the presence of high-concentration *S. mutans* and *Lactobacillus*, both at 4 and 12 weeks in the CAs and FAs groups. The effect of time was also not significant on this variable.

In contrast, Oikonomou et al.[14] obtained in their meta-analysis for a 3 and 6-month follow-up period that adult patients treated with aligners had a lower risk for the presence of *S. mutans* and *Lactobacilli*. Although in the adolescents group, the difference was insignificant between the CAs and FAs groups, in this case, the evaluation was carried out at the beginning of treatment after just 1 month.

In our work we also performed a meta-analysis on the variable mass of biofilm by combining 2 studies that reported the values after 1 month into treatment. Our findings show a statistically significant difference in biofilm mass in patients wearing CAs than in patients with FAs, being lower in those with CAs.

Regarding incipient caries/WSL, in our meta-analysis with 2 included studies, we have found that at the end of treatment (9–24 months), aligners patients have ten times less risk of presenting new WSLs than conventional fixed appliance patients. Our results are consistent with those of Albhaisi et al.,[24] who reported that those wearing CAs presented a lower risk of developing white spots, fewer lesions, and less mineral loss, but with a greater extension than the FAs group. In patients in the FAs group, lesions were more prevalent but smaller and had greater mineral loss than in the CAs group.

Our systematic review and meta-analysis analyzed the existing evidence on periodontal health indicators, oral microbiota, and pre-cavitated enamel lesions. We can consider that only a few studies on these topics have been published that could be quantitatively synthesized, and a thorough assessment of the overall impact of CAs on oral health indicators is, therefore, difficult. Since orthodontic treatments last over time, analyzing the influence of treatment modalities on oral health indicators should be considered extremely important. Meta-regression highlighted the behavior of oral health variables over time.

The small number of randomized studies with high-quality designs that were included in the meta-analysis can be regarded as one of the main limitations of the current study. Moreover, most of the included studies were non-randomized and observational. It should be considered that even if high-quality RCTs are regarded as the gold standard among clinical trials, high-quality cohort studies can also be adequate to study this topic. It should be considered that the choice of orthodontic appliances strongly depends on the patients' socioeconomic background and esthetic requirements. It is challenging to randomly distribute patients into various therapy groups unless the study has external financial funding. Furthermore, the quality assessment underlined how the most prevalent bias was related to “blinding”, unavoidable due to the nature of the appliance being both FAs and CAs visible to the participants and the personnel involved in the study. Moreover, many indexes and a lack of standardization made it difficult to combine them in a quantitative synthesis when assessing periodontal health.

To our knowledge, this is the first meta-regression conducted on this topic. Among the strengths, we can mention the thorough search process among 3 different databases, which allowed us to access most of the published studies that addressed our research question. More than half of the meta-analyses presented slight or no heterogeneity, and no publication bias was detected.

CONCLUSIONS

The findings of this systematic review, meta-analysis and meta-regression suggest that CA patients present better oral health indicators and OHRQoL than FA patients.

The periodontal indicators analyzed show significantly better values in patients treated with CAs, with moderate to large effect sizes. Both the plaque and the bleeding index show a significant tendency to improve throughout treatment with CAs.

The risk of developing WSLs at the end of treatment is ten times lower in the CAs group.

CA patients have a lower biofilm mass compared to those treated with FAs. However, no differences were found in the percentage of patients with high *S. mutans* and *Lactobacillus* counts.

Clear aligners treatment shows a lower impact on OHRQoL than the treatment with fixed appliances.

AUTHOR CONTRIBUTIONS

Conceptualization: ASLR, MAM, JMMC, DG. Data curation: ASLR, JMMC. Formal analysis: JMMC, DG. Methodology: JMMC, JEIC, DG. Supervision: MAM, JMMC, DG. Writing–original draft: ASLR, JMMC. Writing–review & editing: ASLR, MAM, JEIC, JMMC, DG.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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SUPPLEMENTARY MATERIAL

Supplementary data is available at https://doi.org/10.4041/kjod22.272.

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