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Adverse effects of clear aligner orthodontic treatment – a literary review

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Abstract

Background and aim: Orthodontic treatment with clear aligners has been increasingly popular since introduction in the late 1990´s. This literary review is aimed to study the adverse effects in connection to clear aligner treatment regarding white spot lesions, root resorption, periodontal status, pain and discomfort.

Material and methods: Search in the PubMed, Cochrane Library and Embase databases gave 1144 initial titles, and after removal of duplicates and reviewing for exclusion criteria resulted in a final amount of 30 articles. Inclusion criteria were healthy patients with aligner treatment. Keywords were: clear aligner (CA), Invisalign, white spot lesions (WSL), root resorption (RR), periodontal status (PERIO), pain and discomfort (P&D). Endnote was used for organizing articles and excluding duplicates.

Results: Clear aligner treatment was presented to generate significantly less lesions (compared to fixed appliances treatment (6.2 vs. 8.3 lesions/patient); $p < 0.05$)). However, CA lesions were larger in area but shallower. Prevalence of root-resorption was significantly lower in a CA group compared to a fixed appliance group (56% vs. 82%; $p < 0.001$). Periodontal pocket depth was found to be significantly less on average in CA patients compared to FA patients in 5/6 articles. Pain and discomfort levels were significantly lower among CA patients than FA patients during the first week after initiation of treatment.

Conclusion: This literary review clearly indicates that clear aligner treatment has less adverse effects regarding white spot lesions, root resorption, periodontal risk factors, and pain and discomfort compared to conventional fixed appliance treatment.

Introduction

Orthodontic treatment is used to correct malocclusions, caused by dentoalveolar and skeletal discrepancies. Orthodontic appliances have been found among Greek and Etruscan artifacts (1). However, removable and fixed orthodontic appliances were first introduced to a wider audience by Kingsley and Angle in the late 19th century (2). The first aligner treatment was introduced by Kesling in 1945 and consisted of a series of a rubber-based tooth positioner appliances intended to gradually correct misaligned teeth. Fixed appliances (FA) treatment with brackets and arch wires have been dominating over removable appliances treatment during the last decades. Due to computer aided design and computer aided manufacturing technique (CAD-CAM), removable clear aligner treatment has gained popularity in recent years (3) and is considered as a more esthetical alternative to buccally placed fixed appliances (4).

Before the introduction of CAD-CAM technique, the production of clear aligner was labor intensive. Clear thermoplastic appliance was manufactured on multiple series of plaster casts where the teeth were separated from the socket and progressively positioned into an ideal occlusion. A series of clear plastic aligners were fabricated on these casts for the patient to wear and gradually move irregular teeth into the desired position (5, p. 258).

Today the computerized production process (CAD-CAM) of clear aligner starts with chairside direct scanning of patient's teeth and alveolar ridges. The scanning of the jaws is sent to a laboratory together with a prescription plan made by a dentist or orthodontist. A computer-aided design (CAD) software is used to create a series of virtual models, in which the teeth are progressively moved to the desired position in the final model (5, 6). When the virtual models are approved by the referring dentist or orthodontist, a series of aligners are produced by using computer-aided manufacturing technique (CAM). The aligners follow the stages of the treatment plan, and each aligner is worn full-time for 2 weeks in general (5, 7).

There are now several companies offering variations of clear aligner (CA) treatment. Invisalign® and Essix® are two companies using in office scanning technique and the aligners are checked at dental appointments by professionals. Invisalign Align Technology (Invisalign®) created the first sequence of aligners in late 1990s that could correct more complex malocclusions in adults, teens, and children (8) and has dominated the market since (5).

Byte®, Candid Co®, ALIGNERCO®, and Smileunion® are some companies providing so called "home aligners" where impressions of the teeth are taken by the patient, then mailed to the supplier, and reviewed by an orthodontic team. A series of clear aligners are produced using CAD-CAM technique and are then delivered to the patient. Each set should be worn for one week and full-time (9,10, 11). SmileDirectClub® is a home aligner company where scanning of the patient's teeth is made at "Smileshops" (12), and series of aligners are delivered to the customer.

Several recent studies on "in office clear aligner treatment" have claimed that clear aligners produce less white spot lesions (WSL) compared to fixed appliance treatment (13, 14, 15). Fang et al. have stated that root resorption cannot be avoided with clear aligner, however the incidence and severity is lower after clear aligner treatment compared to fixed appliance treatment (16). Periodontal health variables and oral hygiene have also been shown to be better in patients undergoing clear aligner treatment compared to fixed appliance treatment (17). Aligner users have also been reported to have less pain and discomfort compared to patients treated with fixed appliances (18).

Due to the increased popularity of clear aligners, we wanted to gain more knowledge about potential adverse effects with this type of treatment. This thesis is an overview on important adverse effects related to orthodontic treatment, such as white spot lesions (WSL), orthodontically induced apical root resorption (RR), periodontal conditions (PERIO) and pain and discomfort (P&D). Several studies and reviews have discussed one or a few of clear aligner treatment adverse effects, but to our knowledge none have yet presented a literature review on all major adverse effects.

Therefore, the aim of this thesis is to present a synopsis of adverse effects after clear aligner treatment and compare these to adverse effects of fixed appliance treatment.

Material and method

Literature search

We started a wide literature search in June 2021 (ended in October 2021) to identify titles evaluating adverse effects in connection to orthodontic clear aligner treatment. Three electronic databases MEDLINE via PubMed, Cochrane Library and Embase were used with the restriction that articles should be in English. The literary search was done individually by (UBA and BM) and the results compared to improve correct number of articles.
The search syntaxes used in PubMed and Cochrane Library were: “Clear aligner/s or Invisalign and adverse effect”, “Clear aligner/s or Invisalign and root resorption”, “Clear aligner/s or Invisalign and discomfort”, “Clear aligner/s or Invisalign and periodontal health”, “Clear aligner/s or Invisalign and white spot lesion”. The syntax used in Embase was ”orthodontic aligner” since no hit was generated using the terms from the other two databases. We started the search using truncation (*) after each adverse effect. However, comparing search results with and without truncation, revealed that the alternative without truncation gave the most accurate and highest number of hits and therefor was the obvious choice.

Inclusion criteria were orthodontic treatment with all kinds of clear aligners regardless of the patient’s age. We excluded the following titles and articles: case reports, non human studies, studies on non generally healthy patients, titles and articles with patients in active periodontal treatment, having sleep apnea symptoms and/or need of surgery.

Data handling and analysis

All selected titles were imported to separate endnote libraries according to database. Libraries were merged after removal of duplicates within databases, while duplicates between databases were removed thereafter. Titles and articles were screened individually by the researchers (UBA and BM), concerning the inclusion/exclusion criteria, using abstracts and titles. The result was discussed and further categorized into different groups regarding the adverse effects of interest presented in aims.
These adverse effects were:
White Spot Lesions (WSL) which included risk of and demineralization, bacterial and salivary status. Orthodontically induced apical Root Resorption (RR). Periodontal conditions (PERIO) including plaque index, gingival index, probing depths and bleeding on probing.

Pain and discomfort (P&D) reporting experiences of pain and discomfort in connection to aligner treatment.

Main reasons for exclusion were titles and abstracts concerning "other orthodontic appliances", "other adverse effects" and "non- dental" articles amounting to 80% of the 704 discarded scientific papers. Excluded articles were organized in Endnote groups relating to their content read from title and abstract for potential later use of additional information. A substantial number of excluded articles related to sleep apnea and surgical treatment and some involved patients with active periodontal treatment. Systematic reviews were filed separately in Endnote for use in the discussion (Fig. 1: flowchart).

Titles and abstracts for included articles were critically analyzed by both researchers independently and discussed with the supervisor resulting in 85 titles and abstracts, which after assessment and discussion ended up in 23 full-text articles. Manual search in reference lists of the 23 included articles supplied another 7 articles in the final analysis (Fig. 1: flowchart). The 30 articles were categorized and organized based on the aims (WSL, RR, PERIO and P&D) to enhance analysis using an Excel program with columns describing the articles by type of study, year, country, sample size, age and gender of participants, statistical methods, results and conclusions (Table 1). After reading and discussing the articles the researchers (UBA & BM) and supervisor (AS) concluded that the disparate domains of outcome variables and different study designs made quality grading of the articles less valuable and was omitted.

Three of the articles were fully or partially supported by the Align research award program (19, 20, 21). One article was awarded by clear aligner international research award (22).

The term fixed appliance (FA) was used for different kinds of fixed appliances tested in the studies (conventional brackets, self-ligating, low-friction brackets and lingual appliance) and clear aligner (CA) for Invisalign and other types of clear aligners**.** The term root resorption (RR) was used to include what was called EARR (external apical root resorption) or as OIEARR (orthodontically induced external apical root resorption) in the articles.

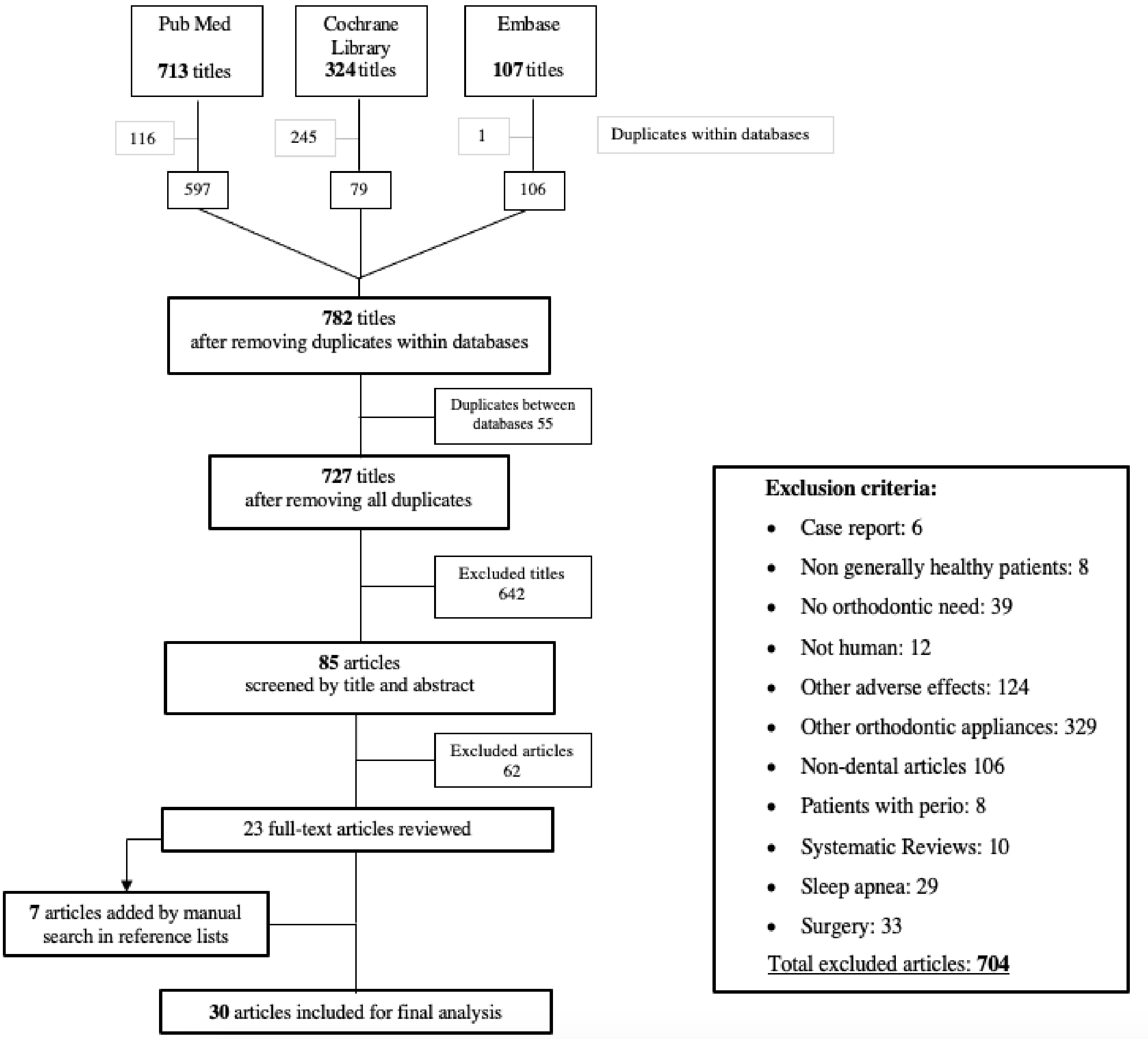

Figure 1. Flowchart: selection process for collecting information to the literary review

Table 1. Basedata for the reviewed articles (n=30)

Article ref. nr.	Adverse effect	Authors	Year	Journal	Country	Subjects *Females/Males*	Groups n	Age (year)	Type of study	Stat. method
23	WSL	Azeem et al.	2017	JWFO	Pakistan	25 *13/12*		14-18	Cohort	
24	WSL	Sifakakis et al.	2018	Prog Orthod	Greece	30 *17/13*	CA 15 FA 15	12-18	Case control	M-W
14	WSL	Buschang et al.	2019	Angle Orthod	USA	450 *285/165*	CA244 FA 206	18-44	Case control	$\chi 2$
15	WSL	Mummolo et al.	2020	Clin Exp Dent RES	Italy	90 *34/56*	CA 30 FA 30	16-25	Case control	$\chi 2$ ANOVA
25	WSL	Tektas et al.	2020	MDPI	Switzerland	6		30-35	Case control	K-W
13	WSL	Albhaisi et al.	2020	AJO-DO	Jordan	42 *33/9*	CA 23 FA 19	17-24	RCT	
26	WSL	Yan et al.	2021	Curr. Microbiol	China	8		18-25	Cohort	ANOVA
22	RR	Iglesias-Linares et al.	2016	Angle Orthod	Spain	372 *219/153*		mean 27.69 ± 13.6	Case control	M-W
30	RR	Gay et al.	2017	Prog Orthod	Italy	71 *46/25*		18-71	Cohort	
29	RR	Aman et al.	2017	AJO-DO	USA	160 *104/56*		mean 34 ± 16	Cohort	
31	RR	Yi et al.	2018	J Dent. Sci	China	80 *60/20*	CA 40 FA 40	mean 22.54	Case control	T $\chi 2$
28	RR	Li et al.	2020	Prog Orthod	China	70 *49/21*	CA 35 FA 35	mean 23.61 ± 7.03	Case control	T $\chi 2$
27	RR	Liu et al.	2021	Angle Orthod	China	40 *20/20*		24.1	Cohort	
36	PERIO	Miethke et al.	2005	J Orofac Orthop	Germany	60 *43/17*	CA 30 FA 30	18-51	Case control	M-W F W
33	PERIO	Miethke et al.	2007	J Orofac Orthop	Germany	60	CA 30, FA 30 (lingual)	16-48	Case control	M-W F W
34	PERIO	Karkhanechi et al.	2013	Angle Orthod	USA	42 *28/14*	CA 20 FA 22	18-44	Case control	ANCOVA
35	PERIO	Abbate et al.	2015	J Orofac Orthop	Italy	47	CA 22 FA 25	10-18	RCT	T
37	PERIO	Azaripour et al.	2015	BMC oral health	Germany	100 *73/27*	CA 50 FA 50	11-62	Case control	
32	PERIO	Levrini et al.	2015	Eur. J. Dent.	Italy	77 *52/25*	CA 32 FA 35 CTL 10	16-30	Case control	M-W
19	PERIO	Chhibber et al.	2018	AJO-DO	USA	61 *41/30*	CA 27 FA 44	14-20	RCT	t-test
21	PERIO	Zhao et al.	2019	Oral Dis	China	25 *22/3*		20-35	Cohort	M-W
38	P&D	Shalish et al.	2012	Eur. J. Orthod	Israel	68 *45/23*	CA 21 FA 28 LA 19	18-60	Case control	MANOVA ANOVA, Bph
42	P&D	Fujiyama et al.	2014	Prog Orthod	USA	145 *96/49*	CA 38 FA 55 CA+FA 52	mean 25.2 ± 6.5	Case control	ANOVA
41	P&D	White et al.	2017	Angle Orthod	USA	41 *24/17*	CA 23, FA 18		RCT	M-W
43	P&D	Flores-Mir et al.	2018	AJO-DO	Canada	122 *89/33*	CA, FA		Case control	MANOVA
18	P&D	Diddige et al.	2020	Med. Pharm. Rep.	India	36 *18/18*	CA 12, FA 12, SL 12	18-30	RCT	ANOVA T
40	P&D	Alajmi et al.	2020	Med Princ Pract	Kuwait	60 *41/19*	CA 30, FA 30	18-50	Case control	$\chi 2$ F
20	P&D	Gao et al.	2021	Eur. J. Orthod	China	110 *84/26*	CA 55, FA 55	mean 24.6 ± 5.20	Case control	ANOVA

39	P&D	Antonio-Zancajo et al.	2020	J. Clin. Med.	Spain	120 *66/54*	CA 30, FA 30, LA 30, LF 30	30 ± 7.5	Case control	ANOVA, M-W F,W
44	P&D	Fraundorf et al.	2021	Angle Orthod	USA	44 *33/11*	CA 24, FA 20	CA 34.8 FA 38.9	Case control	T W

CA: clear aligner treatment FA: fixed appliance treatment LA: lingual appliance treatment SL: self-ligating appliance treatment
LF: low friction appliance treatment CTL: control group
ANOVA: Analysis of variance ANCOVA: Analysis of covariance MANOVA: Multivariate analysis of variance
T: t-test M-W: Mann-Whitney test K-W: Kruskal Walli´s test χ2: Chi-square test F: Friedman's test W: Wilcoxon's test
F: Fisher's exact test Bph: Bonferroni post hoc tests

Results

Electronic search in the three databases produced 1144 titles. Duplicates within and between databases were removed, resulting in 727 remaining titles. Based on inclusion and exclusion criteria, 642 titles were excluded after screening. Subsequently 85 articles were assessed by title and abstract, resulting in 23 eligible full-text articles. Furthermore, seven additional articles were included after manual search in included articles reference lists, leading to a total of 30 included articles for the final analysis (Figure 1) (Table 1).

White spot lesions

Seven articles, published between 2017 and 2021, were included relating the topic of WSL or risk of developing WSL (1 RCT, 4 case control- and 2 cohort studies)

Three articles (23, 13, 14) evaluated prevalence and incidence of WSL. Two with Quantitative Light-induced Fluorescence (QLF) images and one with digital photos. The first QLF study evaluated incidence (newly developed) of WSLs before and after clear aligner treatment and found an incidence of < 3% (23). The second QLF study showed that the CA-group developed significantly less new lesions compared to the FA group after 3 months of treatment (6.2 vs. 8.3 lesions/patient; p < .05). However, new lesions in CA-group were larger but shallower compared to the fixed appliances (FA) group (13). More plaque accumulation was found in the FA-group compared with the CA-group (13).

The study using digital photos showed that patients treated with CA developed significantly less WSLs compared to patients treated with FA (14). This study also showed that both groups developed more WSLs on maxillary compared to mandibular teeth. The incidence of WSL for different groups of teeth in the maxilla was: canines 7.3%, lateral incisors 6% and central incisors 2.9%. The corresponding number in the mandible was: canines 7.1%, lateral incisors 2.6% and central incisors 2.2% (14).

Two studies (15, 24) compared prevalence of cariogenic bacteria (S. mutans, L. acidophilus, and S. sanguinis) together with plaque (PI)-index and gingival (GI)-index between groups treated with clear aligner and fixed appliance. Sifakakis et al. (24) found no difference in the salivary levels of S. mutans or L. acidophilus after 2 weeks and after one month of treatment with these two appliances. However, patients treated with clear aligners had lower salivary S. sanguinis levels than those treated with fixed appliances. They also found statistically significant lower levels of both plaque and gingivitis scores in the aligner group compared to the fixed appliance group.

Mummolo et al. (15) found that 10% of CA patients and 40% of FA patients were subjected to bacterial levels leading to high risk of developing caries after 6 months of treatment. As for PI, the clear aligner group stayed on 0 throughout the study while FA patients presented a significant increase after 3 and 6 months.

The remaining two studies examined bacterial adhesion on different clear aligner materials (25) and changes in flora during the first 24 hours of usage (26). Tektas et al. (25) observed no significant differences in initial microbial attachment or biofilm formation between the four tested aligner materials or in comparison to enamel surfaces and conventional metal brackets. Yan et al. (26) revealed that the microbial composition during the first 24 hours of clear aligner use changed with an increased number of Lactobacillales, Bacteroidales and Streptococcus. This led them to the conclusion that clear aligners should be cleaned after 12 h or at least within 24 h of usage.

Rot resorption

Root resorption (RR) was evaluated in six articles published between 2016 and 2021 (3 case control- and 3 cohort studies). Cone Beam Computed Tomography (CBCT) was used to assess root resorption by loss of volume and length in three studies (27, 28, 29). Two of these (27, 28) presented the prevalence of root resorption and the last established the incidence (29).

A reduction in root volume (27) and length (28) was found after treatment with clear aligners. The incisors investigated by CBCT technique showed 71% mild (<10%), 28.4% moderate (10-20%), and 0.6% severe (>20%) reduction of root length after CA treatment (27). However, the prevalence of RR in incisors and canines was significantly lower in the clear aligner group compared to the fixed appliance group (56.3% vs. 82.1%; $p < .001$) (28).

Aman et al. (29) found that the incidence and percentage of change of RR (root shortening) in the incisors in patients ongoing clear aligner treatment was significantly lower for Class I compared to Class II malocclusions with less than a half-step molar Class II (4.20%, $p < .01$). Subjects with mild crowding presented significantly less percentage of change in root resorption compared to those with severe crowding (2.72%, $p = 0.03$).

Three studies (22, 30, 31) used panoramic radiographs for assessment of root length/shortening. Gay et al. (30) investigated root resorption in all incisors, canines, upper first premolars, first molars. They found that the incidence of reduction in root length was mild in 26% of CA patients, moderate in 12% and severe in 3.7% of CA patients. Also 41% of CA patients had a minimum of one tooth affected by 20% root reduction (30). Yi et al. (31) found significantly less root resorption in all incisors in clear aligner patients compared to fixed appliance patients ($5.13 \pm 2.81\%$ vs. $6.97 \pm 3.67\%$; $p < .001$). On the other hand, Iglasias-Linares et al. (22) found that CA patients were more prone to RR than FA patients (OR: 2.097; $P = 0.002$). However, there were no significant association between radiographic, genetic or clinical factors for predisposition to root resorption, regardless treatment type (CA or FA).

Periodontal status

Eight articles, published between 2005 and 2019, relating to periodontal conditions were included (3 RCT's, 1 cohort- and 4 case control studies).

Six articles (21, 32-36) used assessment of pocket depth (PD) as outcome variable and two articles evaluated plaque index (PI), gingival index (GI) and bleeding on probing (BOP) (37, 19). Five articles found significant lower average PD in patients treated with CA compared to patients treated with FA after 3-months (1.3 mm vs. 1.7 mm; $p < .05$) (32), 9-months (2.31mm vs. 2.50 mm; $p < .05$) (33), and after one year (2.5 mm vs. 3 mm; $p < .003$) (34), (2.7 mm vs. 3.8 mm; $p < .05$) (35). Furthermore, no deterioration of PD was observed in a cohort study of CA-patients after 6-months (21). The remaining study found no significant difference in PD after approximately 6-months clear aligner treatment in comparison to fixed appliances treatment (2.31 vs. 2.54; p value >.05) (36).

Chhibber et al. (19) found no significant difference in gingival assessments after 18-months, while Azaripour et al. (37) found significant better gingival conditions in CA-patients, BOP and GI, than patients under FA treatment.

Six articles found significantly lower PI values in patients treated with CA compared to FA (21, 32-36), and 4 articles found an improvement in plaque index for CA patients throughout the study (21, 33-35).

Four articles evaluated microbial changes in addition to clinical assessments of periodontal parameters (21, 32, 34, 35). Two RCT studies used a PCR-procedure to investigate presence or absence of periodontopathic bacteria (P. intermedia, A. actinomycetemcomitans, P. gingivalis, Tennerella forsythia) (35, 32). One cohort study characterized and compared salivary microbiome diversity before and after 6-months of CA-treatment by MiSeq sequencing (21), and one case control study utilized the BANA-test (34). Abbate et al. (35) and Levrini et al. (32) found no periodontopathic bacteria in the CA-group, while one patient treated with FA tested positive for A. actinomycetemcomitans (32). Additionally, Levrini et al. (32) found that the CA-group had a significantly lower bacterial concentration compared to FA group ($p < .05$).

MiSeq sequencing revealed no significant changes after 6-months of CA treatment regarding oral biodiversity or salivary microbial community. The only significant difference was a decrease of Prevotella at the 6-months follow up (21). BANA-test showed a significantly higher BANA-score in the FA- group compared to the CA-group of periodontopathogen bacteria (T. denticola, P. gingivalis and T. forsythia) after 6-months of treatment (odds ratio 5.7). However, after 12-months no significant difference could be found (odds ratio 3.8) (34).

Pain and discomfort

Nine articles, published between 2014 and 2021, evaluated pain and discomfort in connection to clear aligner treatment (2 RCT's and 7 case control studies). Pain and discomfort levels, analgesic consumption, satisfaction, oral symptoms/dysfunction and speech performance were evaluated using visual analogue scale (VAS) and questionnaires.

Pain and discomfort in patients treated with CA or FA was studied in 7/9 studies (18, 20, 38, 39, 40, 41, 42).

Pain started four hours after treatment initiation and peaked during the first 24 hours in both CA and FA groups (18, 20), with reported severe pain (VAS 8-10) in 38% of CA patients compared with only 10% in FA patients (38). No statistical significant difference in pain level between CA and FA treatment was found by Shalish et al. (38). Contradicting results were found by Diddige et al. (18) and Antonio-Zancajo et al. (39), were CA patients experienced significantly lower pain levels during the first week compared to FA ($p = 0.001$) (18) and ($p < .01$) (39). Gao et al. did not find any significant difference in pain levels between CA and FA after two weeks of treatment (20).

Alajmi et al. (40) assessed pain duration and different types of pain and found no statistical significant difference in pain duration between CA and FA treatment ($p = 0.052$). CA patients reported more pressure-like pain ($p = 0.016$) while fixed appliance patients experienced throbbing and dull-like pain ($p = 0.037$ and 0.019, respectively).

Forty-five percent of CA patients were found to use analgesics the first 2 days post treatment initiation compared to only 11% in fixed appliance patients during the first day (41). CA patients consumed analgesics between day 1-3 but reported no consumption at day 6.

However, FA reported no consumption at day 4 (38, 41). In contrary, according to Alajmi et al. (40) and Diddige et al. (18) analgesic consumption was reported to be higher in the FA group compared to the CA group after initiation (40) with a significant higher analgesic consumption the first two days in the FA group ($p < .001$) (18).

Discomfort was reported to peak at 24h in both CA and FA (18). However, with significantly higher levels in the FA group compared with CA group (41, 42) between day one until day seven (300-500% vs. 50-100%; $p < .05$) (41). FA treatment also showed significantly higher scores for intensity of pain (63 vs. 33), number of days in pain (4 vs. 2) and discomfort (62 vs. 34) with a significant of $p < .05$ in all the three parameters (42).

The remaining 2/9 studies in this category evaluated satisfaction (43) and speech performance (44). Satisfaction (100%) with treatment was experienced in 47% of CA patients compared to 24% of the FA patient (43). Patients using clear aligners reported more satisfaction with appearance of appliance compared to FA patients (18, 40). However, Diddige et al. (18) findings reached significance ($p < .001$) while Alajmi et al. (40) reported insignificance difference ($p = 0.052$). Fixed appliance patients also reported more disturbance when eating (38, 18, 40) with statistically significance ($p < .001$) (18). Restrictions in types of food consumed and chewing limitations ($p = 0.020$ and 0.001, respectively) were reported by Alajmi et al. (40).

Speech performance was assessed in four studies (18, 38, 40, 44). Significantly more patients using CA reported change in the desired way of speech and speech delivery ($p = 0.003$, $p = 0.035$, respectively) (40). They also showed adaptation to the treatment and had speech articulation errors even after two months (44). Clear aligner patients also showed a moderate change in speech compared with fixed appliance patients, who reported minimal change in speech (44). Two studies found no significance difference between CA and FA groups regarding difficulties in speech (38,18). Speech improved by day 7 in both groups ($p = 0.962$) (18).

Oral symptom i.e. sores on tongue, cheek or lip, bad taste/smell, and food accumulation after two weeks were rated higher in the FA group then in the CA group on a scale from 1-5 (1.81 vs. 1.27, $p = 0.047$) (38). Alajmi et al. found statistically more mucosal ulcerations in FA patients ($p = 0.01$) compared to the CA group (40).

Discussion

This literature overview on adverse effects in connection to clear aligner treatment presents recently published studies ranging from 2003 to 2021, with a large geographical spread that makes the results more generalizable.

The three databases were chosen to represent a wide spectrum of clinical implications and patient experiences and ended up in many hits due to a wide search syntax. Remarkable many duplicated titles were found within the Cochrane Library database (76%) but also in the PubMed search (16%). The Embase search on the other hand presented only one duplicate. This was probably caused by a less precise search strategy, which was not individually designed for each database, and the way the EndNote software was used for identifying duplicates. This could have led to early exclusion of relevant titles which is implied by the large number of articles found by manual search of the reference lists. Inclusion criteria were concentrating on the adverse effects by clear aligner treatment mentioned in the aim and exclusion criteria were supposed to rule out other types of orthodontic treatment and disorders and malocclusions of severe character.

Due to the number of outcome variables and differences in study design, quality grading of the articles was regarded as of lesser value and therefor omitted. However, notice have been taken to the different study designs when evaluating the results in the discussion.
Three of the articles were fully or partially supported by the Align research award program (19, 20, 21) One article was awarded by clear aligner international research award (22). This was openly declared and considering the type of study design used and type of publication, funding by Align research may not have affected impartiality.

The results from the selected 30 studies will be discussed in relation to earlier published systematic reviews concentrating on either white spot lesions, root resorption, periodontal status or pain and discomfort.

White spot lesions

When measuring the incidence of white spot lesions, clear aligners had a significantly low incidence. This is due to the ability to remove the CA, gain normal access to all teeth surfaces, and perform proper oral hygiene (14). Lower plaque accumulation has also been detected in CA-patients (24, 15, 13). Likewise, a meta-analysis found lower plaque accumulation in patients under clear aligner treatment (17). Although WSL incidence was lower in CA- compared to FA-treatment, Albhaisi et al. found that newly developed WSL in CA-group was larger in area, but shallower in severity (13). This finding can be explained by the effect of total coverage of teeth surfaces with CA that obstructs the normal saliva flow, which aids buffering and remineralizing properties, and additionally limit the natural cleansing activities by the lips, cheeks, and tongue (45). Moreover, aligner usage for 12- and 24-hours reduces bacterial diversity, decreases pH-levels in the inner surface, and leads to increased levels of cariogenic bacteria (26). Based on these findings, Yan et al. (26) recommends that clear aligners should be cleaned after 12 h or at least within 24 h of usage to avoid enamel demineralization.

Regarding cariogenic bacteria (S.mutans, L. acidophilus, and S. sanguinis) Sifakisis et al. (24) and Mummolo et al. (15) found contradicting results, which may be due to the short duration (1 month vs. 6 months) and age difference (only adolescents vs. adolescents and adults) between the studies. Sifakakis et al. found no difference in the salivary levels of S. mutans or L. acidophilus after 2 weeks and after one month of treatment with CA- and FA in adolescents. However, S. sanguinis levels was lower and decreased throughout study duration in CA-patients. Demineralization and caries development is mainly associated with abundance of S.mutans and L. acidophilus in oral microbiota (46), while S. sanguinis in dental plaque is often associated with dental health (47, 48). Thus, the total teeth coverage by clear aligners leads to lower levels of cariostatic bacteria (S. sanguinis) in adolescents after one month according to Sifakisis et al. (24).

Mummolo et al. (15) found an increase in cariogenic bacterial colonization units (S.mutans and Lactobacilli) in both CA and FA patients. Only FA-patients reached significant levels of colony forming unites (CFU/min >105), which indicates a high risk of caries development, after 3- and 6-months. After 6 months of treatment 10% of CA patients and 40% of FA patients were subjected to bacterial levels leading to high risk of developing caries. Hence, clear aligner treatment seems much less vulnerable than conventional orthodontic treatment with braces (15). Furthermore, no significant differences in initial microbial attachment or biofilm formation have been found between different aligner materials (CA-medium, Co-polyester, Duran and Erkodur) or in comparison to enamel surfaces and conventional metal brackets (25). Consequently, bacterial adhesion seems not to be the problem, but rather the ability to clean the teeth properly.

Root resorption

Studies included in this category were case controls or cohort studies, and a notice should be taken that these studies are known to have lower ranking in the evidence scale.

The incidence, prevalence and severity of root resorption were assessed using either CBCT or panoramic radiographs. CBCT shows three dimensional results and was shown to be more precise in measuring due to its high spatial resolution which can detect root changes in all directions (16, 49, 50.). Panoramic radiographs demonstrates more image distortion with loss of precision (16). Thus, results could be affected by different projections and magnifications and give different measurements (51). However; root-crown length and root-crown ratio were measured and taken into consideration when using panoramic radiographs, according Krieger et al. (51). Although there are used different types of measurement tools, studies suggests that CBCT is more reliable especially when assessing root resorption (52).

Results from this review presents that a higher percentage of CA patients had mild resorption compared with 0.6% who developed severe resorption. It should be noticed that clear aligner treatment are used for more simple cases with milder malocclusion compared with FA (53, 28) and that malocclusion´s severity are a risk factor for root resorption (30, 29).

The incidence and prevalence of root resorption in incisors were significantly lower in clear aligner- compared to fixed appliance patients (27, 28). This may be due to force types in CA treatment being classified as more of light and intermitting forces, as aligner are removed for eating and brushing teeth according to a systematic review by Weltman et al. (54). Light forces allows root cementum to heal, preventing any further resorption (55, 56), in contrary to continuous and heavy forces in fixed appliance treatment (54). Aman et al. (27) presented that heavy forces applied in fixed appliance treatment may cause more resorption to teeth and therefore increase the incidence and severity of RR (27, 54). A meta-analysis by Fang et al. (16) are in agreement with our findings, concluding that clear aligner treatment contributes in RR but is less severe compared to the fixed appliance.

Aman et al. (27) found that patients with class I malocclusion had significantly lower resorption compared to class II patients. The same study presented that crowding was a risk factor for RR, where patients with mild crowding had lower resorption than severe crowding (27). Although there was a significant difference, the percentage of difference between the groups was only 2% which may be irrelevant clinically (10).

All six included studies regarding RR (22, 27, 28, 29, 30, 31) examined root resorption in incisors (centrals, laterals) either in maxillary/mandibulary jaws or in both jaws. However, incisors are shown to be most affected by RR (51, 27). Gay et al. (30) evaluated other affected teeth, and found that 41% of patients had at least one tooth affected of RR. Moreover, it is difficult to study multi-rooted teeth in panoramic radiographs, that may be the reason why most of the studies only included incisors (31).

In 5/6 of included studies in this category; age and gender did not have any influence and was not a confounding factor (22, 28, 29, 30, 31). Only Aman et al. (27) found a significant difference between women and men, with lower values in women compared to men. However, risk factor for root resorption were treatment duration, location of teeth, extraction cases and malocclusions types and severity (58,29,30). Furthermore, according to our findings CA is associated with less root resorption.

Periodontal status

When assessing periodontal status, the most often utilized diagnostic parameter for evaluating periodontal disease is pocket depth (59), while bleeding on probing (BOP) and gingival index are diagnostic parameter for gingival inflammation (60). Moreover, the presence of periopathogenic bacteria such as P. gingivalis, T. denticola, T. forsythia, A.

actinomycetemcomitans, and Prevotella intermedia is significantly associated with periodontal disease (61).

Five out of six included studies in this review regarding periodontal status presented that patients treated with clear aligners had superior periodontal health in terms of pocket depth, gingival index, and bleeding on probing measurements (21, 32-35). This finding agrees with a meta-analysis by Jiang et al. (17). The pilot study by Miethke and Vogt showed no significant difference between CA- and FA-patients in GI, BOP and PD after 3-months follow up (36). Although patients wore their appliances for minimum of 6 months, the only significant difference between groups were PI. (36) This may be due to the lack of periodontal health evaluation, and proper oral hygiene instruction prior to treatment start.

Chhibber et al. (19) found no significant difference in periodontal parameters (PI, GI and BOP) between patients treated with CA and patients treated with FA in the long term (18 months). However, CA-patients exhibited better GI and BOP scores in the short term (9 months). The inconsistency between short- and long-term effects can be explained by FA-participants habit alteration after periodontal evaluation 9-month follow up and feedback from their practitioner (19). As mentioned earlier, due to the ability to gain full teeth access with removable clear aligner, patients had significantly lower (32-36), and even improvement in plaque index scores contrary to fixed appliances (21, 33, 35, 36).

Periodontopathogen bacteria quantity and quality assessment exhibited lower values in CA-patients. Zhao et al. (21) utilized MiSeq sequencing and detected significant decrease in Prevotella quantity at 6-months follow up of patients undergoing CA-treatment. This may indicate less risk to develop periodontitis and oral health improvement in CA treated patients, since Prevotella abundance is associated with periodontitis (61). Karkhanechi et al. (34) found significant higher levels of T. denticola, P. gingivalis, and T. forsythia in patients under fixed appliance treatment when compared to CA-patients at 6-months follow up, but the bacterial levels failed to reach significance at 12-months assessment. According to Karkhanechi et al. it is unclear if the inconsistency between short- and long-term bacterial levels is due to an actual decrease in bacterial quantity or to decreased study power after 12-months. However, clear aligner patients presented superiority when assessing periodontopathogens.

Pain and discomfort

Pain is a common adverse effect in orthodontic treatment and arises four hours after initiation and decreases through seven days (62). Two studies reported a peak in pain levels after 24 hours (18, 20) which is consistent with finding from earlier studies (63-65).

One study (38) showed that CA patients initially experienced more severe pain compared to FA patients, Shalish et al. reported that this finding might be due the mechanical forces implemented at the initial stages of CA treatment, while treatment technique in the fixed appliance patients were more gradual but lighter forces (38). In contrast, earlier studies have found that FA patients experienced greater pain in the first week compared to CA patients (62, 66-68), which is similar to the findings in two included articles in our review (18, 39).

VAS was mainly used to assess pain levels. This is a visual method allowing patients to report their pain on a 10-cm scale from 1-10. New studies are critical to this measurement method and consider it as of less reliability and validity compared to other methods (69-71). Despite that, VAS is still used for assessing pain levels. A notice should be taken that pain are also influenced by several individual factors and this may contribute to affect the results of pain measurements (68).

Analgesic consumption was reported by four of our included studies (18, 38, 40, 41) and shown to be larger in FA- compared to CA patients in three studies (18, 40, 41). However, analgesics were used only for a few days. No information on instructions to the patients were presented in any of the articles. Contrary results were found in one study (38), reporting that CA- consumed more analgesic than FA patients. Moreover, FA also experienced more throbbing and dull-like pain compared to CA patients who experienced more pressure-like pain (40). Pressure-like pain may be more accepted, giving a possible reason for a lower consumption of medication in CA group (40).

A systematic review by Cardaso et al. presented similar findings to our review, reporting that only one study with higher pain levels and higher use of analgesics in the CA group (68). The remaining studies assessed in the systematic review reported higher pain levels and analgesic consumption in the FA as compared with CA.

Discomfort exhibited a similar trend as pain and was significantly greater in FA than CA patients during the first week (41, 42) and coincides with the results by Sergl et al. (66). Deformation of the aligners was one of reasons for patient´s discomfort (42). CA treatment showed less discomfort due to its ability to being removed and allowing the tissue to reorganize before compressive forces are reapplied (41).

Greater percentage of clear aligner patients reported 100% satisfaction compared to FA patients (18, 43). Satisfaction was connected to better aesthetics, eating function and the ability to remove appliance (18, 68). In addition, significantly higher levels of oral symptoms was observed in fixed appliance patients (38, 68). This is an expected finding since metal brackets in FAs irritates the mucosal tissue giving more symptoms, with a significantly more mucosal ulcerations in the FA group (40). Regarding speech, two studies reported more speech difficulties in CA patients compared to FA with a significant difference. CA also showed mild change in speech, unlike FA that showed moderate change (40, 44).

This literature review evaluated articles regarding pain and discomfort levels in short time period. A study by White et al. (41) evaluated P&D in two months period. CA patients had lower P&D levels after one month adjustment compared to FA patients. However, there was no significant difference after subsequent two months in both groups (41). Further studies are needed for long-term evaluation of pain levels.

Conclusion

This literary review clearly indicates that clear aligner treatment has less adverse effects regarding white spot lesions, root resorption, periodontal risk factors and pain and discomfort compared to conventional fixed appliance treatment.

Figures and tables

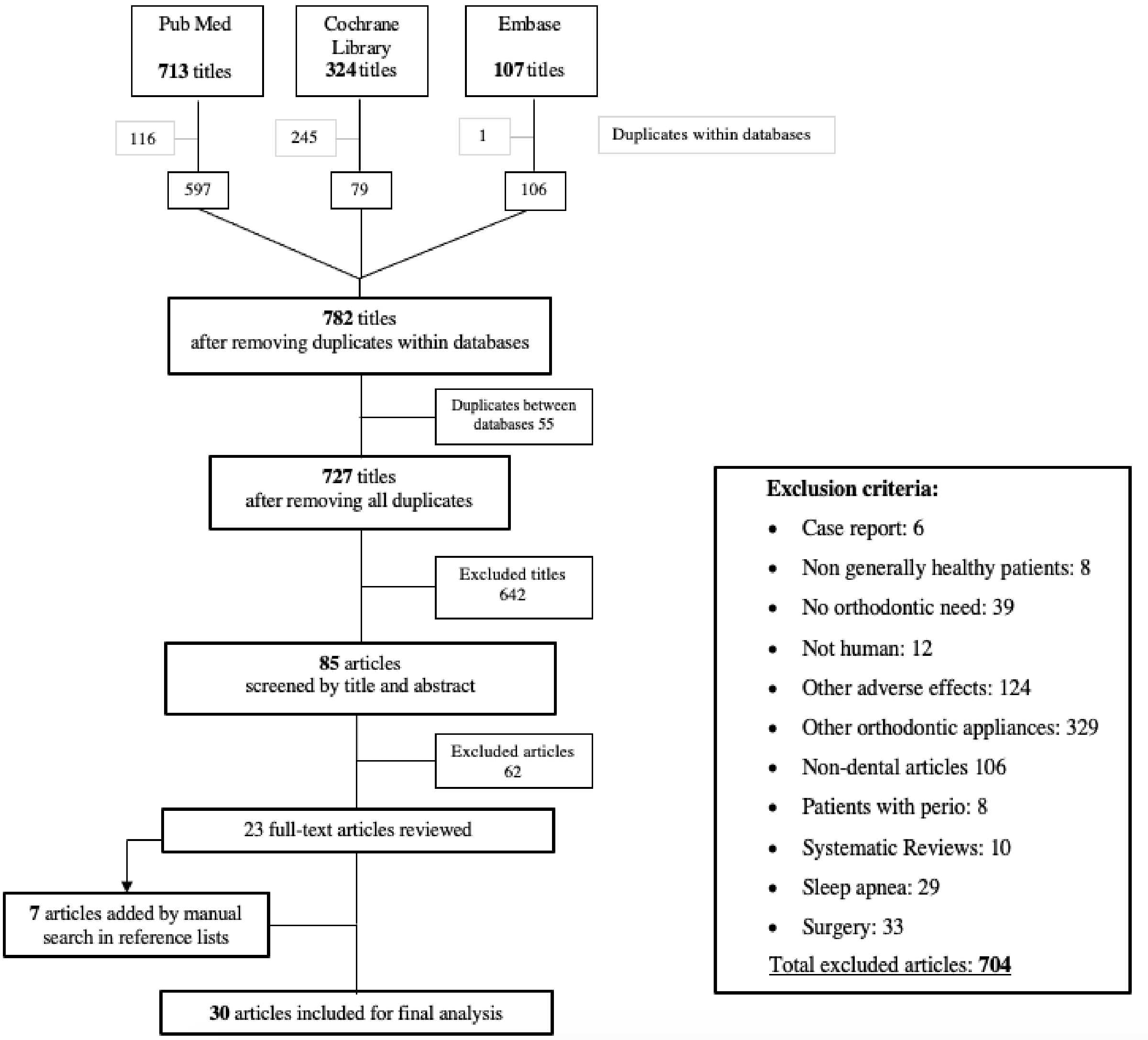

Figure 1. Selection process for collecting information to the literary review

Table 1. Basedata for the reviewed articles (n=30)

Article ref. nr.	Adverse effect	Authors	Year	Journal	Country	Subjects *Females/Males*	Groups n	Age (year)	Type of study	Stat. method
23	WSL	Azeem et al.	2017	JWFO	Pakistan	25 *13/12*		14-18	Cohort	
24	WSL	Sifakakis et al.	2018	Prog Orthod	Greece	30 *17/13*	CA 15 FA 15	12-18	Case control	M-W
14	WSL	Buschang et al.	2019	Angle Orthod	USA	450 *285/165*	CA244 FA 206	18-44	Case control	χ2
15	WSL	Mummolo et al.	2020	Clin Exp Dent RES	Italy	90 *34/56*	CA 30 FA 30	16-25	Case control	χ2 ANOVA
25	WSL	Tektas et al.	2020	MDPI	Switzerland	6		30-35	Case control	K-W
13	WSL	Albhaisi et al.	2020	AJO-DO	Jordan	42 *33/9*	CA 23 FA 19	17-24	RCT	
26	WSL	Yan et al.	2021	Curr. Microbiol	China	8		18-25	Cohort	ANOVA
22	RR	Iglesias-Linares et al.	2016	Angle Orthod	Spain	372 *219/153*		mean 27.69 ± 13.6	Case control	M-W
30	RR	Gay et al.	2017	Prog Orthod	Italy	71 *46/25*		18-71	Cohort	
29	RR	Aman et al.	2017	AJO-DO	USA	160 *104/56*		mean 34 ± 16	Cohort	
31	RR	Yi et al.	2018	J Dent. Sci	China	80 *60/20*	CA 40 FA 40	mean 22.54	Case control	T χ2
28	RR	Li et al.	2020	Prog Orthod	China	70 *49/21*	CA 35 FA 35	mean 23.61 ± 7.03	Case control	T χ2
27	RR	Liu et al.	2021	Angle Orthod	China	40 *20/20*		24.1	Cohort	
36	PERIO	Miethke et al.	2005	J Orofac Orthop	Germany	60 *43/17*	CA 30 FA 30	18-51	Case control	M-W F W
33	PERIO	Miethke et al.	2007	J Orofac Orthop	Germany	60	CA 30, FA 30 (lingual)	16-48	Case control	M-W F W
34	PERIO	Karkhanechi et al.	2013	Angle Orthod	USA	42 *28/14*	CA 20 FA 22	18-44	Case control	ANCOVA
35	PERIO	Abbate et al.	2015	J Orofac Orthop	Italy	47	CA 22 FA 25	10-18	RCT	T
37	PERIO	Azaripour et al.	2015	BMC oral health	Germany	100 *73/27*	CA 50 FA 50	11-62	Case control	
32	PERIO	Levrini et al.	2015	Eur. J. Dent.	Italy	77 *52/25*	CA 32 FA 35 CTL 10	16-30	Case control	M-W
19	PERIO	Chhibber et al.	2018	AJO-DO	USA	61 *41/30*	CA 27 FA 44	14-20	RCT	t-test
21	PERIO	Zhao et al.	2019	Oral Dis	China	25 *22/3*		20-35	Cohort	M-W
38	P&D	Shalish et al.	2012	Eur. J. Orthod	Israel	68 *45/23*	CA 21 FA 28 LA 19	18-60	Case control	MANOVA ANOVA, Bph
42	P&D	Fujiyama et al.	2014	Prog Orthod	USA	145 *96/49*	CA 38 FA 55 CA+FA 52	mean 25.2 ± 6.5	Case control	ANOVA
41	P&D	White et al.	2017	Angle Orthod	USA	41 *24/17*	CA 23, FA 18		RCT	M-W
43	P&D	Flores-Mir et al.	2018	AJO-DO	Canada	122 *89/33*	CA, FA		Case control	MANOVA
18	P&D	Diddige et al.	2020	Med. Pharm. Rep.	India	36 *18/18*	CA 12, FA 12, SL 12	18-30	RCT	ANOVA T
40	P&D	Alajmi et al.	2020	Med Princ Pract	Kuwait	60 *41/19*	CA 30, FA 30	18-50	Case control	χ2 F
20	P&D	Gao et al.	2021	Eur. J. Orthod	China	110 *84/26*	CA 55, FA 55	mean 24.6 ± 5.20	Case control	ANOVA

39	P&D	Antonio-Zancajo et al.	2020	J. Clin. Med.	Spain	120 *66/54*	CA 30, FA 30, LA 30, LF 30	30 ± 7.5	Case control	ANOVA, M-W F,W
44	P&D	Fraundorf et al.	2021	Angle Orthod	USA	44 *33/11*	CA 24, FA 20	CA 34.8 FA 38.9	Case control	T W

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Appendix I

Excluded titles and abstracts based on the following exclusion categories

n (PubMed + Cochrane + Embase)

Exclusion criteria:

- Case report: 6 (1+0+5)
- Non generally healthy patients: 8(4+0+4)
- No orthodontic need: 39 (37+0+2)
- Not human: 12 (11+0+1)
- Other adverse effects: 124 (22+34+68)
- Other orthodontic appliances: 329 (321+4+4)
- Non-dental articles 106 (106+0+0)
- Patients with perio: 8 (7+1+0)
- Systematic Reviews: 10 (7+1+2)
- Sleep apnea: 29 (29+0+0)
- Surgery: 33 (27+2+4)

Total excluded articles: 704 (572+42+90)