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ANNA ILIADI

Materials and Clinical Aspects of Orthodontic Treatment with Aligners

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This thesis is dedicated to my parents
and
to those who inspired it and will not read it

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ABSTRACT

Background: The use of orthodontic aligners to treat a variety of malocclusions has considerably increased in the last years. Yet evidence on forces and moments generated across difference aligners types, their efficacy and adverse effects relative to conventional fixed orthodontic appliances, accuracy obtained on specific tooth movements, the effect of aligner cleaners on their composition and mechanical properties and changes in the morphology, roughness and composition of attachment surfaces in contact with the aligners remain unclear.

Aim: The aim of the present thesis was to study: (i) the existing evidence on forces exerted by aligners, (ii) the efficacy of aligners compared to orthodontic treatment with fixed appliances, (iii) the accuracy of specific tooth movements, (iv) the effects of aligner cleaners and (v) the aligner/attachment surfaces during orthodontic treatment with aligners.

Methods: Two systematic reviews with meta-analyses were conducted to address the issues regarding the existing evidence on forces and moments generated by aligner type appliances and aligner efficacy and adverse effects relative to conventional treatment with fixed appliances. Seven and eight databases were searched without limitations for each topic respectively. Risk of bias assessment was based on the Cochrane Risk of Bias tool in all cases. A total of 13 in-vitro studies deemed eligible for inclusion and 2 were included in the quantitative synthesis for the former subject, whereas 11 studies (4 randomized/7 non-randomized) and 3 meta-analyses were conducted for the latter subject. Accuracy obtained from aligner treatment on specific tooth movements was measured by superimposing the predicted and achieved models over the initial ones in 20 Class I adult patients on posterior teeth. Moreover, the impact of three aligner cleaners was tested employing two alkaline peroxide solutions (Retainer Brite - RB; Retainer Cleaner - RC) and one peroxide-free (Steraligner - ST) on two different aligner companies, Clear Aligner (polyester) and Invisalign(polyester-urethane) for a two-week period. The acidity, changes in the chemical composition and changes in Martens Hardness (HM), elastic modulus (E_{IT}), elastic index (n_{IT}) and relaxation (R_{IT}) were studied. Finally, attachments bonded with 2 different light-cured composite resins (sculptable and flowable) to 20 zirconia CAD/CAM frames and corresponding aligners, were examined before and after aligner removal and reseating in water, under (i) a stereomicroscope to identify morphological alterations, (ii) an optical profiler to measure the 3D-roughness parameters and (iii) by attenuated total reflection FTIR spectroscopy (ATR-FTIR) to determine changes in the molecular composition and

degree of C=C conversion.

Results: When palatal tipping of the upper central incisor through PET-G aligners was considered, aligner thickness of 0.5, 0.625 or 0.75 mm was not associated with a significantly different moment to force (M/F) ratio. Aligner thickness does not appear to possess a significant role in forces and moments generated by clear aligners under specific settings, while the most commonly examined tooth movements are tipping and rotation. Moderate quality evidence indicated that treatment with orthodontic aligners is associated with worse occlusal outcome with the American Board of Orthodontics Objective Grading System and more patients with unacceptable results. No significant differences were seen for treatment duration. Horizontal movements of all incisors seemed to be accurate, with small (0.20-0.25 mm) or insignificant differences between predicted and achieved amounts. Vertical movements and particularly intrusions of maxillary central incisors were found to be less accurate, with a median difference of 1.5 mm ($p<0.001$). All achieved rotations were significantly smaller than those predicted, with the maxillary canines exhibiting the greatest difference of 3.05^{o} ($p<0.001$). RB and RC aligner cleaners were weakly acidic (pH = 6.3), whereas ST was mildly acidic (pH = 4.8). The ATR-FTIR analysis demonstrated evidence of acidic hydrolysis of Clear Aligner in ST and Invisalign in RB. The IIT-derived properties of Invisalign were not affected by the cleaners. However, for Clear Aligner a significant change was found in HM (all cleaners), n_{IT} (all cleaners) and R_{IT} (RB, ST). Finally, characteristic abrasion-induced defects by removal and reseating of the aligners were detected without significant changes in the roughness parameters (control-tested), but with significant higher values in Sdr between materials within control or tested groups. The sculptable material appeared superior in terms of morphology and retention characteristics. Insignificant differences in the C=C conversion were found in the groups tested. However, in some specimens strong peaks or irreversibly absorbed water were detected indicating hydrolytic susceptibility of the superficial composite zone.

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ABBREVIATIONS

ABO	American Board of Orthodontics
ABO-OGS	American Board of Orthodontics objective grading system
ATR-FTIR	Attenuated Total Reflectance Fourier Transform Infrared Spectrometry
BPA	Bisphenol-A
C	Clear Aligners
Cis	Confidence Intervals
CO	Control
DI	Discrepancy Index
EARR	External Apical Root Resorption
EIT	Indentation modulus
EPA	U.S. Environmental Protection Agency
ERs	Estrogenic receptors
EVA	Ethylene vinyl acetate
GRADE	Grades of Recommendations Assessment
HM	Martens Hardness
I	Invisalign
I^2	Relative heterogeneity
IIT	Instrumented indentation testing
IPR	Interproximal Reduction
M/F	Moment to force ratio
MCF-7	Human breast cancer cell
MD	Mean difference
MDA-MB-231	Epithelial human breast cancer cells
n_{IT}	Elastic index
NNT	Numbers Needed to Treat
OHRQoL	Oral health-related quality of life
PAR	Peer Assessment Rating scores
PC	Polycarbonate
PE	Polyethylene
PET-G	Glycol-modified polyethylene terephthalate
PICOS	Participants-Intervention-Comparison-Outcome- Study design
PP	Polypropylene
PU	Polyurethane
RB	Retain Brite
RC	Retain Cleaner
RCT	Randomized control trial

R_{IT}	Indentation relaxation
ROBINS-I	Risk Of Bias In Non-randomised Studies of Interventions
RR	Relative risk
SMD	Standardized mean difference
ST	Steraligner
Tg	Glass transition temperature
THR	Thyroid hormone receptor
TPU	Thermoplastic polyurethanes
$\tau 2$	Absolute heterogeneity

ORIGINAL PUBLICATIONS

This dissertation is mainly based on the following four original publications and an unpublished study:

I. Iliadi A, Koletsi D, Eliades T. Forces and moments generated by aligner-type appliances for orthodontic tooth movement: A systematic review and meta-analysis. Orthodontics and Craniofacial Research. 2019;22:248-258.

II. Charalampakis O, Iliadi A, Ueno H, Oliver DR, Kim KB. Accuracy of clear aligners: A retrospective study of patients who needed refinement. American Journal of Orthodontic and Dentofacial Orthopedics. 2018;154:47-54.

III. Papageorgiou S, Koletsi D, Iliadi A, Peltomaki T, Eliades T. Treatment outcome with orthodontic aligners and fixed appliances: a systematic review with meta-analyses. European Journal of Orthodontics. 2020;42:331-343.

IV. Iliadi A, Enzler V, Polychronis G, Peltomaki T, Zinelis S, Eliades T. Effect of cleansers on the composition and mechanical properties of orthodontic aligners in vitro. Progress in Orthodontics. 2022;15:23:54.

The studies are referred to in the text by their roman numerals.

AUTHOR'S CONTRIBUTION

Publication I Wrote the manuscript, performed study selection, data collection, data synthesis, assessed the risk of bias within studies and contributed to the final manuscript

Publication II Designed the study, collected the sample, interpreted the results, performed the statistical analysis and wrote the manuscript.

Publication III Wrote the manuscript, performed study selection, data collection, data synthesis and assessed the risk of bias within studies. All authors discussed the results and contributed to the final manuscript.

Publication IV Planned and performed the experiments, contributed to sample preparation and wrote the manuscript.

1. INTRODUCTION

The concept of fabricating aligners on setup casts for orthodontic tooth movement dates back to 1945[1]. This revolutionary development was driven mainly by the increasing demand for invisible orthodontics and aesthetic considerations, primarily across adult patients. By the end of the 1990s, two thermoplastic aligner systems were introduced allowing for a wide range of tooth movement[2]. The first implemented setups comprising of tooth displacements requiring a sequence of 3 aligners per setup step. The second, allowed for setup steps to be reduced, so that stiffer aligners could be employed[3]. Stereolithographic models and digital setups were implemented, allowing for only one initial impression.

Fuelled by aggressive marketing campaigns from manufacturers, a growing interest for such methods for invisible orthodontics has been reported, especially among adult patients[3]. A survey of Australian orthodontists in 2013 indicated that 73% of responders had used aligners to treat at least one case in the last year, with a median of 8 aligner cases[4]. A similar survey among Irish orthodontists in 2014 reported that 19% of them often used aligners to treat adult patients[5]. A large 2014 survey among orthodontic specialists in the USA revealed that 89% of them had treated at least one case with aligners (compared to 76% in 2008) and with a median of 22 cases/year (compared to 12 cases/year in 2008), but only few orthodontists used aligners for premolar extraction cases (9%-18%)[6]. Additionally, another survey among members of the European Aligner Society indicated that 45% of orthodontists believed that aligners limit orthodontic treatment outcomes (even though the respective percentage among general dentists was only 5%)[7]. Such data might indicate that the initial surge of aligner treatment during its early years of fame might have now given its place to a more mature evaluation of this treatment modality, as an alternative to the gold standard of conventional fixed appliances, based on long-term outcomes. Contrary to many medical fields, it is a common place in orthodontics that novel marketed products and treatment approaches are clinically adopted based on advertisement policies, apparently without the appropriate clinical evidence to back any claims by the manufacturers[8]. In any case, it is imperative that alternative treatment methods offered to orthodontic patients are based on both the doctor's clinical expertise and solid evidence on the clinical performance of this modality. Ideally, treatment decisions should be based on well-designed and

-reported comparative clinical trials on human patients and systematic reviews / meta-analyses thereof, after meticulous considerations of treatment efficacy and adverse effects[8]. Ample empirical evidence has now been gathered about the importance of proper study design and methodological characteristics that may result in bias[9].

In the last decade several systematic reviews of clinical or observational studies comparing orthodontic aligners with fixed appliances have emerged[10-13]. However, they all present methodological issues that may introduce bias and hamper their ability to draw robust evidence-based recommendations, including: lack of an a priori design / pre-registered protocol[11,12], language bias, inclusion of non-randomized studies with uncontrolled confounding, inclusion of diagnostic accuracy studies comparing aligner treatment outcomes to predicted tooth movements lacking a viable treatment alternative, inadequate handing of the studies' risk of bias, lack of quantitative data synthesis (meta-analysis), improper data synthesis methods, and being outdated[10-13]. Therefore, it is important that clinical practice is informed by a critical appraisal of currently available studies according to the principles of evidence-based medicine.
Furthermore, clinical behaviour of thermoplastic aligner- type appliances is not unaffected by occlusal forces and/ or wear- related properties. The former has been associated with load increases when it comes to rotational moments or intrusive forces[14]. The latter may lead to a considerable force decay and deactivation, which may reach approximately 50 percent after a 2-week period of aligner use[15].

Notwithstanding, forces and moments generated by such aligner-type appliances on teeth remain largely unknown to clinicians. The force-delivery properties of thermoplastic orthodontic aligners in terms of setup magnitude have been compared in several studies. It has been stated that setup increments should preferably range between 0.2 and 0.5 mm, depending on the type of thermoplastic material used[16]. Other studies investigated the forces and moments applied on teeth by thermoplastic aligners in a series of movements. During mesiodistal rotation forces were exceeding the suggested load of 20 Nmm[5]. Similar findings were confirmed for intrusion, tipping, and bodily movement[17,19,20].

2. REVIEW OF THE LITERATURE

2.1 TYPES OF CLEAR ALIGNERS

The last 20 years, orthodontic aligners have enjoyed great popularity addressing patients demand for esthetic orthodontic treatment[21]. Their clear transparent appearance and the ability to remove them when eating while maintaining oral hygiene, combined with the reduced chair-side time has made them exceedingly desirable especially among adult patients[22].

Originally, clear aligners were used to treat minor irregularities of tooth position or as final stages during orthodontic treatment[23]. Nowadays, the increasing demand for invisible orthodontics and aesthetic considerations, combined with the developments in the field of aligners eventually led to their use for the treatment of moderate to severe malocclusions, with various degrees of clinical effectiveness. Today, after the expiry of Invisalign's patent, a number of clear aligner brands prevail such as ClearAligner™, Clear path™, Clear Image Aligners™, SLX Clear Aligners, Sure Smile, Clarity Aligners, Spark, ClearCorrect™Smilelign, MTM Clear-Aligner™, Nimrodental Clear aligner™, Nuvola®, Simplifive™, Fantasmino® [24-27].

Initially, aligner companies such as Align technology developed an indirect fabrication technique, where dental models from various materials such as resin and stone were created based on precise impressions or digital scans of the patient's teeth[24,25]. According to this method, individual teeth are electronically or manually separated and moved gradually and sequentially to their desired positions[26]. Each stage of treatment is converted into a physical model where plastic sheets are placed over, heated and formed into custom-made clear aligners either with applied air pressure or under vacuum[24,27]. The final product is transparent with a scalloped or straight-line finish (Figure 1, 2)[23]. By the end of the 1990s, two novel thermoplastic aligner systems were introduced allowing for a wide range of tooth movements. The first implemented setups comprising tooth displacements between 0.5 and 1 mm[2,28,29], which required a sequence of 3 aligners per setup step, with increasing thickness. The second, allowed for setup steps to be reduced to approximately 0.2 mm, so that stiffer aligners could be employed[3,28,29]. Stereolithographic models and digital setups were implemented, allowing for only one initial impression. Despite the increased demand aligner treatment is considered till today an expensive option, which may discourage patients and clinicians alike.

The development of direct 3D printing technology introduced an innovation to the manufacturing process evading the dental lab since the fabrication of the actual dental model is no longer necessary[30]. Electronically stored 3D dental data obtain through dental scans are transferred to the corresponding 3D fabrication system stereolithography, fused deposition modelling, direct pellet–fused deposition, selective laser sintering, multi-jet photocured polymer process or continuous liquid interface production technology[31,32]. Despite major benefits such as low-cost treatment and same day delivery further research on the material's mechanical properties and biocompatibility is still required[33].

Figure 1. Clear aligner made from glycol-modified polyethylene terephthalate (PET-G). Note the gingival edge width.


Figure 2. Clear aligner (Invisalign) made from polyester-urethane (PU). Note the scalloped gingival edges.

2.2 CLEAR ALIGNER MATERIALS

2.2.1 Chemical composition

In general, aligners are fabricated out of viscoelastic materials and more precisely of resin polymers including mainly glycol-modified polyethylene terephthalate (PET-G), polyurethane (PU), polypropylene (PP), polycarbonate (PC), thermoplastic polyurethanes (TPU), ethylene vinyl acetate (EVA) and polyethylene (PE) which are translucent and difficult to detect with naked eye[34]. The sequential aligners are usually fabricated out of polyester-urethane (PU) or polyethylene terephthalate glycol (PET-G)[3]. In 2013 Align Technology introduced a new generation of Invisalign aligner material called SmartTrack. According to the manufacturer, it contains thermoplastic polyurethane with an integrated elastomer. This highly elastic material can exert low and continuous forces over a long period of time[35].

2.2.2 Mechanical properties

Ideally, an orthodontic aligner should exert light and constant forces to avoid overloading of teeth during orthodontic tooth movement[36]. For this to be achieved, the materials used to fabricate aligners should exhibit substantial linear elastic behaviour with a high yield point and a relatively flat relaxation curve to ensure constant and continuous forces over time[37]. Furthermore, aligner hardness should be high enough to withstand intraoral wear, while the final product should be biocompatible.

The mechanical behaviour of orthodontic aligners is strongly affected by their construction material, temperature alterations, and humidity during the manufacturing process[35]. Viscoelastic materials demonstrate a time-dependent response during loading. At constant loads creep occurs, thus increasing the strain of such materials over time. Moreover, stresses developed under constant strain are decreased over time, a phenomenon called relaxation[37]. Other time dependent responses include different expression of hardness and elastic modulus resulting in poor wear resistance and endurance mainly to the occlusal and incisal surfaces of the aligners after short-term use[38]. In order to identify the aforementioned properties, mechanical tests are utilized. Due to the small size of the specimens, instead of conventional mechanical testing, instrumented indentation testing (IIT) is used to measure a variety of mechanical properties through a simple hardness measurement[39] (Figure 3). Research has shown that there are distinct variations in hardness between different thermoplastic materials used for aligner manufacturing. Under clinical conditions, Invisalign aligners (PU) have higher hardness and modulus values and exhibit superior wear resistance when compared to other PET-G materials although they are slightly more brittle and have lesser creep resistance[40]. Notable differences were also spotted among several PET-G thermoplastic materials. The different molecular weight of the various PET-G polymers combined with the thermoforming effect caused from the rapid cooling of the thermoplastic materials on plaster models, might be the two main factors responsible for the differences observed in hardness[40]. Furthermore, according to in vitro studies, PET-G materials exhibit greater wear resistance when compared to materials based on PP[41].

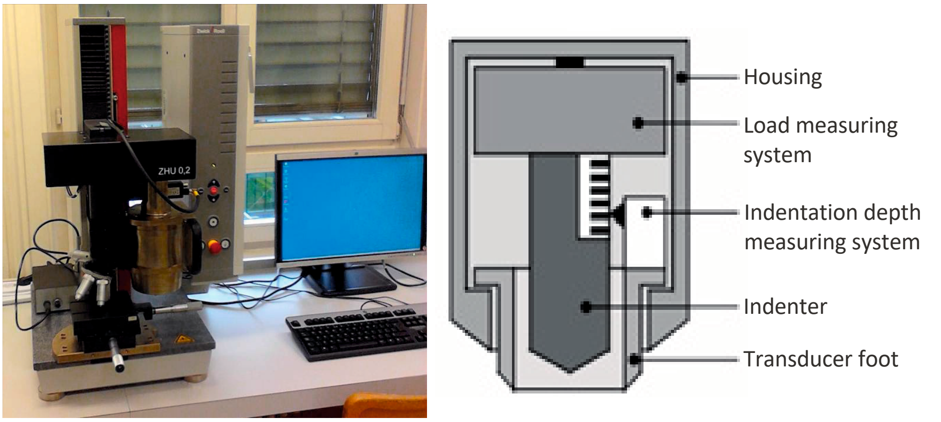

Figure 3. Instrumented indentation testing (IIT) measures a variety of mechanical properties such as hardness, elastic modulus, creep and relaxation based on force-indentation depth curves

The degree of crystallinity also affects the mechanical properties of polymer materials. An essential parameter in this regard is the glass transition temperature (Tg), which causes the materials to soften quickly when exceeded. Thus, the mechanical properties of polymers having a Tg lower than room temperature may be considerably influenced by temperature changes[42,43]. To ensure that orthodontic aligners can deliver a constant force while under strain, it's important that the materials used during the construction process possess a high modulus of elasticity. This allows thinner aligners to apply the same force as thicker aligners made of lower modulus materials. A study published in 2013 revealed that the Invisalign aligners' indentation modulus values were between 2,000 and 2,500 MPa[41]. This falls in line with the values reported for other thermoplastic orthodontic appliances and is higher than that of other PETG materials[40]. Nonetheless, PU aligners demonstrated a higher elastic index, which suggests that the material is more brittle, and displayed higher indentation creep. Therefore, under constant occlusal forces, this type of aligner is more likely to deform and reduce the magnitude of the orthodontic forces applied[40].

2.2.3 Intraoral alterations on aligner mechanical properties

Water absorption

Water can cause thermoplastic materials to expand and undergo several chemical changes, leading to irreversible degradation of the polymer's mechanical properties. This can occur through water absorption from humidity in the air, immersion in water, or intraoral application[44]. Studies have shown that water absorption can also contribute to stress relaxation in thermoplastic materials, which is why low water absorption rates are ideal for aligners[44]. While water primarily penetrates the amorphous regions of polymers, it can also affect the crystalline domains of the polymer[45]. The plasticizing effect of water can be explained both by the rupture of hydrogen bonds within and between polymer chains, resulting in the formation of water/polymer bonds and through the modification of the free volume of the polymer[46,47](Figure 4). The role of water may also involve washing out soluble products or undergoing a chemical reaction[48].

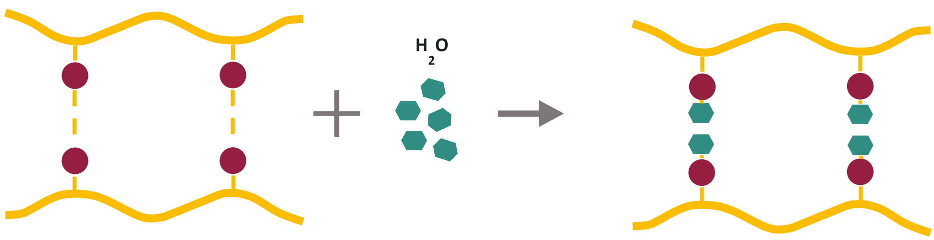

Figure 4. Rupture of hydrogen bonds within polymer chains, resulting in the formation of water/polymer bonds

Tests for water absorption typically involve measuring the weight gain of thermoplastic specimens after they are immersed in distilled water. While these experiments can provide valuable insights into water absorption in vitro, it is important to note that the oral environment is much more complex in terms of both chemistry and usage. Aligners are periodically removed and reinserted, and this usage can impact water absorption in ways that may not be fully captured by in vitro experiments.

Water absorption of eight different commercial thermoplastic products has been studied during a two-week evaluation period. The results indicated that water absorption of all aligners increased over time, with some reaching a plateau during the measurement period. Among the products tested, PU aligners exhibited the highest water absorption after 1 and 14 days, whereas PE aligners demonstrated the smallest linear expansion rate. Generally, amorphous plastics demonstrated higher water absorption rates than crystalline plastics[42].

Further research conducted concerning two commonly used PET-G products and several PET-G/PC/TPU polymer blends showed high water absorption rate, which was followed by a slowdown and a plateau after 2 weeks of immersion with a weight increase of approximately 0.5% to 0.8%. These findings suggest that the use of PETG/PC/TPU blends may be advantageous in aligner fabrication, as they exhibit lower water absorption rates and better dimensional stability compared to PET-G products[36].

Stress relaxation of five different commercial orthodontic thermoplastic materials has been compared in a water bath and in an atmospheric environment. The results indicated that residual stress within all materials decreased over time, although the process was significantly accelerated in the 37°C water bath. Moreover, the materials delivered only 40% to 65% of their initial forces following a 3-hour immersion in a 37°C water bath[49].

The aforementioned findings suggest that the type of polymer used in aligner manufacturing can impact water absorption and may ultimately affect the aligner performance, leading to a significant decrease in the initial forces generated.

Transparency

As far as esthetics is concerned, the primary advantage of orthodontic aligners is their high degree of transparency, which needs to remain stable throughout a 2-week use of each aligner set. As such, manufacturers recommend the removal of aligners prior to eating or drinking. A study utilized visual inspection to assess the perceptible colour change of three commercial aligner products following in vitro staining with coffee, black tea, and red wine. The results showed that all three types of aligners demonstrated relatively stable colour over a 12-hour immersion period. However, the Invisalign aligners exhibited slight staining from coffee after 7 days of immersion[50]. Another research found that aligner transparency decreased when the layer thickness increases, a finding documented also in PET-G blended with PU aligners[51].

2.2.4 Oral microbiome

Fixed orthodontic appliances remain the gold standard in orthodontic treatment through the years. Despite their benefits they can also pose a risk to oral hygiene by potentially compromising the integrity of both tooth enamel and periodontal tissues due to plaque build-up and colonization by oral microbes[52]. The installation of these appliances can make it challenging to follow standard oral hygiene practices and can lead to changes in the oral microflora, including a decrease in pH levels and an increase in plaque accumulation and bacterial affinity to metallic surfaces due to electrostatic reactions[53]. Moreover, the installation of these appliances creates new areas for bacteria to grow, leading to an increase in local streptococci levels appearing in the saliva and around the appliances[54].

Various factors associated with thermoplastic appliances can affect their efficacy in the oral environment. Surface morphology may contribute to bacterial adhesion, resulting in higher levels of salivary bacteria. The surface of aligners is not entirely smooth but exhibits microabrasions and irregularities which may contribute to bacterial adhesion and biofilm accumulation (Figures 5a, 5b)[55]. Thus, salivary proteins that adhere to the surface of aligners are compositionally different from those on enamel surfaces, resulting in a variation of microorganisms within the subsequent biofilm. However, recent research indicates that using a vibrating bath with a cleaning solution protocol is more effective in reducing biofilm adherence than regular brushing or immersing the aligner in chlorhexidine mouthwash[56].

(a)

(b)

Figure 5. Images of retrieved aligner surfaces which are not completely smooth but exhibit microabrasions and irregularities(a). This may contribute to bacterial adhesion making the appliance more conducive to calculus accumulation(b).

Although orthodontic aligners themselves do not create new areas for bacterial accumulation, they may indirectly affect periodontal health. The amount of gingival coverage provided by aligners varies across different systems and may directly influence periodontal parameters and microbial colonization. While Invisalign aligners do not have significant gingival coverage, other aligner systems are trimmed to overlap the attached gingiva to improve retention. This approach is intended to enhance aligner retention, but it may come at the expense of periodontal implications. Moreover, the manufacturing process also plays a critical role on aligner surface. Pressure-forming techniques, which involve higher pressures than vacuum-forming, may affect to a certain extent the level of detail of the inner fitting surface of the aligner[27].

The placement of conventional fixed orthodontic appliances, especially orthodontic bands, in proximity to gingiva may initiate adverse effects and have a significant impact to the overall periodontal health of the patient. In most cases, due to the plaque retentive properties and surface morphology of such appliances, inflammation will develop when combined with inadequate oral hygiene. Orthodontic appliances with a higher tendency of plaque accumulation create conditions that make it easier for the balance in the plaque composition to shift towards a more complex configuration. Over time, more gram-negative, anaerobic, and periodontopathic bacteria can be found in this complex biofilm. If left unchecked, these bacteria can cause further inflammation of the gingival tissues. This effect is particularly noticeable in interdental regions where bacteria are even more protected from removal forces[57].

Caries and periodontal disease are caused by specific pathogenic bacteria. The main contributors to the development of dental caries are Streptococcus mutans and Streptococcus sobrinus, whose presence increases the risk of enamel demineralization[58]. After placement of orthodontic attachments, an increase in the levels of S. mutans and Lactobacillus in the oral cavity has been observed. Several findings suggest a positive correlation between dental caries and the degree of infection with these bacteria species[59]. Limited evidence exists regarding the use of thermoplastic aligners as an alternative to fixed appliances regarding oral hygiene. Recessed and sheltered areas of aligners, such as the cusp tips and attachment dimples, may provide a conducive environment for bacterial growth and colonization compared to flat surfaces[55]. A systematic review published in 2015 stated that patients treated with aligners presented superior periodontal health and improvement in oral hygiene compared to patients treated with traditional fixed appliances[10]. Furthermore, a retrospective study revealed that the periodontal parameters of patients treated with thermoplastic aligners could be better than those treated with lingual fixed appliances[60]. Nevertheless, a recent randomized trial reported that while patients initially treated with thermoplastic aligners had better periodontal parameters than those treated with conventional or self-ligating fixed appliances, the overall impact of appliance choice on periodontal health during treatment was not significant[61].

2.2.5 Biological considerations

Orthodontic materials, such as bonding adhesives, plastic polycarbonate brackets, elastomeric materials, and aligners, share the same monomers. A significant concern regarding their use is the potential leaching of chemical substances known as xenoestrogens into the immediate environment surrounding the product[62]. These substances can induce a biological response similar to that of estrogen hormones. Xenoestrogens typically exert their effects by binding to classic estrogenic receptors (ERs) such as ERα and ERβ at subtoxic concentrations, thereby inducing estrogenic signals that may alter gene expression. This mechanism of action is commonly referred to as estrogenicity[63,64]. Bisphenol-A (BPA) is a material of particular concern, as it is widely used in the manufacturing of plastic products[65]. BPA has a similar chemical structure to 17β-estradiol and may therefore have comparable effects on the body. This similarity in structure has raised concerns about the potential health risks associated with BPA exposure[66,67]. Infants are particularly vulnerable to the effects of BPA exposure because they lack enzymes capable of metabolizing BPA into its biologically inert form. As a result, infants may experience higher levels of BPA in their bodies compared to adults[68].

BPA has been demonstrated to have adverse biological effects mainly in experimental animals, including hormonal-related effects such as early puberty in females and feminization in males[69]. Additionally, BPA acts as a thyroid hormone receptor (THR) antagonist, disrupting THR-mediated transcription[70]. BPA exposure has also been linked to a higher risk of breast cancer in females and prostate cancer in males[69,71]. Moreover, BPA has been shown to induce calcium influx, resulting in the release of prolactin and its associated behavioural effects[72]. Other detrimental effects of BPA include the development of hyperglycemia and insulin tolerance[73], elevation of oxidative stress mediators[74], upregulation of the cAMP response element-binding factor (which inhibits apoptosis), potential cytotoxic effects like an immune reaction to material exposure, cell cycle disturbance, cell apoptosis, and induction of mutagenesis or carcinogenesis[65,75]. BPA exposure has also been associated with neurobehavioral problems like autism and attention deficit hyperactivity disorder[76]. The presumed "safe" dose of BPA, as established by the U.S. Environmental Protection Agency (EPA) reference dose and the Food and Drug Administration's acceptable daily intake dose, is 50 μg/kg/day[67,73,77]. However, studies have shown that adverse effects can occur with BPA doses below the aforementioned daily level[78,79].

The potential risk of estrogenic effects in orthodontics arises from the fact that dimethacrylate based restorative materials contain BPA adducts, which can result from the breakdown of BPA derivatives caused by nonspecific esterases and other salivary enzymes that attack the resin matrix[80]. It has been stated that the quantity of BPA released from orthodontic adhesives is lower than the threshold required to induce a biologic reaction[68,81]. On the contrary, other studies confirm the cytotoxic effects of orthodontic adhesives[82-84]. A study evaluating the estrogenic effects of chemically cured no-mix and light-cured orthodontic adhesive resins in a simulated orthodontic environment found that there was no indication of breast cancer cell proliferation stimulation. This suggests that the components of orthodontic adhesive eluents do not exhibit any estrogenic properties[68]. Moreover, it was found that the degree of polymerization of the adhesive is critical in order to ensure minimum BPA release[85].

As far as aligners are concerned, notable differences have been detected in the morphology of used PU (Invisalign) aligners compared to unused ones. The differences include abrasion at the cusp tips, integument adsorption at stagnation sites and localized calcification of the biofilm[35] (Figures 5a, 5b). Traceable amounts of biologically active substances were detected in ethanol aging solution after immersion of aligner specimens for two weeks at 23°C although they did not have any cytotoxic effect on human gingival fibroblasts neither exhibited any discernible estrogenic activity when tested on breast cancer cells[35,86]. Another study indicated that epithelial cell exposure to eluates derived from immersing Invisalign plastic in saline solution resulted in alteration in cell viability, membrane permeability and adhesion[75].

Prolonged use of vacuum-formed aligners as retainers can cause material degradation over time[87]. A study discovered statistically significant levels of BPA in the saliva of patients using vacuum-formed retainers as opposed to those using Hawley or comparable appliances[6]. Potential cytotoxic and estrogenic effects of Vivera retainers (retainers manufactured by Align technology) has been studied by evaluating the biological behaviours of retainers retrieved after four-week use. The findings revealed that no significant increase in human breast cancer (MCF-

7) cell proliferation was caused. As anticipated, p-estradiol had a strong stimulating effect on human breast cancer (MCF-7) cell proliferation, but no effects were observed on epithelial human breast cancer cells (MDA-MB-231)[88].

A potential risk of BPA release during orthodontic treatment with aligners could be related to the bonding of attachments to facilitate precise orientation of the crown, mainly by increasing rotational control of the teeth. These attachments consist of three-dimensional composite resin blocks. The characteristics of their bulk structure may make them prone to hydrolytic degradation, which could potentially affect the amount of monomer release. Furthermore, bonded attachments have a significantly higher hardness than the materials used for aligners. As a result, when the aligners are removed or seated, the friction developed between the polymer and the composite, could result in the attrition of the softer polymer. The potential release of materials from the aligners due to this unfavourable outcome has also not been studied.

Finally, the potential release of materials due to hydrolytic degradation as well as the mechanical behaviour of aligners when patients consume warm or hot beverages while wearing them, has also not been studied.

2.3 ORTHODONTIC TREATMENT USING CLEAR ALIGNERS

2.3.1 Benefits with aligner treatment

The advantages of utilizing clear aligner in orthodontic therapy include aesthetics, comfort, better oral hygiene and reduced chair time[3]. Adults undergoing treatment with aligners experience reduced discomfort and fewer detrimental impacts on their daily lives compared to individuals with traditional fixed appliances[89,90]. During the initial week of orthodontic treatment, patients treated with aligners used less pain medication than individuals treated with fixed appliances[89]. Moreover, adolescents exhibited a positive attitude towards aligners, with the majority not restricting their food choices, avoid communication, or feel self-conscious while in treatment[91]. After 3 months of aligner treatment, approximately 70% of individuals had rarely or never encountered discomfort, and roughly 80% had rarely or never resorted to pain relief medication. As the treatment advanced, patients noted even less discomfort[91]. In addition, clear aligners yield positive outcomes for periodontal health when compared to fixed appliance treatment[92]. Over a 24-month period, teenagers undergoing treatment with aligners experienced a reduction of 15.1% in the plaque index for the maxilla and 16.6% for the mandible[91].

2.3.2 Limitations with aligner treatment

In recent years, several methods such as the American Board of Orthodontics objective grading system (ABO-OGS) and the Peer Assessment Rating scores (PAR) have been employed in order to assess the quality of aligner treatment[93-95]. Although excellent clinical outcomes can be achieved with clear aligners, there is still uncertainty regarding the predictability, parameters, and clinical efficacy and efficiency of aligner treatment. The limitations of aligner therapy have been extensively discussed in literature, where the effectiveness of such treatment remains a topic of debate[3,11,13]. While some clinicians believe that aligners are only suitable for treating mild to moderate malocclusions, others have demonstrated their effectiveness in treating more severe malocclusions[96-98].

There are several possible reasons why teeth may not align to the same degree as the initial plan depiction e.g., Invisalign ClinCheck following an initial course of aligner treatment. These reasons include compromised patient cooperation, problems with the default protocols applied, failure of aligners to achieve 100% of the movements depicted and doctor's lack of experience in creating an effective treatment plan. Additionally, it is crucial to acknowledge that aligner systems are restricted in four dimensions in a manner that does not apply to fixed appliances. In terms of treatment methodology, teeth and any attachments applied to them can be viewed as being equivalent to brackets in fixed appliance treatment, since they both serve as the mean by which force is exerted on the teeth. The force required for teeth movement in aligner treatment is generated by the aligners themselves. In this sense, the series of aligners can be viewed as similar with a full-size, super-elastic arch wire that would be utilized in fixed appliance treatment, except that the aligners are changed periodically throughout treatment instead of being left in place[18]. As such, the ClinCheck plan should be regarded as the equivalent of an arch wire design that is intended to result in the best possible clinical outcome[17]. As stated above, aligner treatment can frequently result in less than satisfactory clinical outcomes, with some of the most common issues being rotations (including those of incisors and premolars), transverse expansion, correction of deep bites, root uprighting and torque[95,98-101]. To bypass these limitations and minimize the need for additional aligners, overcorrections are often integrated into the ClinCheck.

Compared to fixed orthodontic appliances, aligners impose more significant restrictions on tooth movement since dental arches must fit entirely within the three-dimensional confines of the aligner. This results in limited tooth movement according to the exact pace dictated by the instructions given. On the contrary, with fixed appliances, teeth are free to move along the arch at a pace dictated by biological processes, as long as the arch wire is not cinched back and play is allowed in the bracket slot. When there is insufficient space to accommodate the three-dimensional constraints of the aligner, a tooth can become too large to fit, may intrude or stop tracking. This may also occur in cases of expansion[17].

2.3.3 Aligners as retainers

For more than five decades, clear plastic appliances have been employed as retainers. In the late 1950s, Nahoum[102] introduced the first vacuum-formed retainer. Primarily, these retainers did not gain widespread popularity due to reliability issues regarding plastic failing or cracking. Nevertheless, by the early 1990s, specific plastics with mechanical properties more suitable for retainer use were developed. These plastics exhibited less distortion and were less susceptible to cracking. Over the years clear retainers commercially known as "Essix" gained popularity around the world. Nowadays many orthodontists in several countries use them as the first-choice retainers both in the upper and lower jaw[103-105].

Clear plastic retainers are typically made either from polyethylene or polypropylene which both are considered thermoplastic materials or from polyurethane, a thermoset plastic[106]. Polyurethane retainers were created to enhance material characteristics provided by polyethylene and polypropylene retainers, such as better crack and stain resistance, increased transparency, and superior stress retention. However, more independent studies are required to determine the effectiveness of polyurethane retainers when compared to well-established materials like polyethylene and polypropylene retainers[106]. The manufacturing process of clear retainers can be achieved by using pressure or vacuum on plastic sheets, resulting in pressure-formed or vacuum-formed products. However, a digital alternative has emerged that involves taking an intraoral scan or scanning an impression to produce digital virtual models. These virtual models can be used to create study models using a 3D printer. The retainers can then be thermoformed on the 3D printed models[106]. Retainer thickness is relevant to the type of plastic used. A pilot RCT suggested that 1mm retainer thickness is preferable over 0.75mm[107].

Retention is widely considered to be a critical area in orthodontics. Nevertheless, there is a lack of sufficient high-quality evidence to support the optimum retention method, including the use of clear plastic retainers[108]. A clinical trial comparing the use of clear plastic retainers and Hawley retainers, found no statistically significant difference in the stability of intercanine or intermolar widths in both arches[109,110]. Moreover, in a RCT study[112], upper and lower clear plastic retainers were compared with upper and lower bonded retainers. After 1 year, both types of retainers were successfully maintaining a decent level of stability. However, there was slightly more relapse in Little's Irregularity Index in the lower arch with the clear plastic retainer compared to the bonded retainer. Additionally, a greater failure rate of the mandibular bonded retainers compared to the mandibular clear plastic retainer was detected. Another study documented a statistically significant increase in relapse with lower clear retainers when compared to lower bonded retainers, although the differences stated were minor and were characterized as being clinically insignificant[113].

2.4. PATIENT EXPERIENCE WITH CLEAR ALIGNER TREATMENT

2.4.1 Quality of life with clear aligner treatment

The objective of orthodontic treatment is to achieve a balanced, healthy, functional, and esthetic occlusion while also ensuring a harmonious facial appearance. Considering the numerous advantages of orthodontic treatment, it is reasonable to expect that patients' personal opinions regarding their dental aesthetics, facial features, oral health, and functionality would also improve. The effects of self-perceived malocclusion seem to have an impact on a person's psychological and social activities in daily life, expressed as ability to smile, convey emotions, and engage in social interactions[114,115]. Individuals with incisors crowding and significant irregularities in the upper front teeth (> 2 mm) are likely to experience difficulties with smiling, laughing, and showing teeth without feeling embarrassed. Moreover, those with an overjet over 5 mm are nearly four times more likely to experience negative effects on their emotional well-being[115]. In general, studies have indicated that orthodontic treatment can enhance a person's quality of life concerning oral health[116,117]. The use of fixed appliances in orthodontic treatment has been linked to negative effects on several domains of health-related quality of life, including physical function and psychological discomfort[118,119]. Moreover, it has been found that during orthodontic treatment the oral health-related quality of life (OHRQoL) slightly worsens, probably because of the appliance discomfort and appearance[120]. Miller et al. conducted a study using a daily diary to compare the impacts on quality of life during the first week of orthodontic treatment between patients who received aligners and those who received buccal fixed appliances[89]. Throughout the investigation period, individuals in the aligner group reported less adverse effects on overall quality of life. Another study investigated the impact of initial adjustment period on oral dysfunction, eating difficulty and ability to perform daily activities in adult patients wearing buccal or lingual fixed appliances or clear aligners. Patients treated with aligners had the lowest level of oral symptoms compared to the patients in other groups [22,121]. In the follow-up, it was found that aligner use had little effect on oral health-related quality of life during an 8-month investigation period, however in the first 3 months some patients experienced occasional difficulties pronouncing certain words. Nevertheless, majority of the participants reported few problems with their sense of taste, eating, and daily activities, as well as no issues regarding shyness or insecurity caused by wearing the aligners[122].

2.4.2 Pain experience

It is common for orthodontic patients to experience discomfort or a sensation of tension on the teeth[123]. Research indicates that 70% of patients also report pain during orthodontic treatment[124]. Even so, only 15% of orthodontic patients consider the pain significant, and only a minority would discontinue orthodontic treatment because of it[124]. It has been reported that there is a difference in pain perception throughout the day, especially during the first two days following appliance activation, with the difference being greater in female patients[125]. Some patients use medications such as paracetamol or ibuprofen to relieve such pain[126]. Another study concluded that while the relevance of pain during orthodontic treatment with fixed appliances on patients psychosocial and behavioural facets cannot be ignored, clinical and demographic traits play a role in shaping these dimensions. Thus, relying solely on pain intensity might not offer a comprehensive grasp of how pain perception is truly understood[127].

Studies have shown that patients undergoing orthodontic treatment with aligners may experience some pain of mild to moderate severity, particularly during the first 2 to 3 days after starting to use a new pair of aligners. However, this discomfort usually decreases during the subsequent period, and overall, by the end of treatment, pain experience is considered neutral[122,128,129]. Recent advances in orthodontic materials may help reduce the intensity and duration of pain experienced during treatment, as well as the pressure felt during aligner insertion[130].

While some studies suggest that aligner treatment may be associated with less pain during the initial stages of treatment compared to fixed appliances[89,128,131], other studies have not found this to be the case[132]. A recent RCT evaluated the difference in discomfort levels experienced by patients who received aligners and those who received fixed orthodontic appliances. During the initial week of treatment, patients with fixed orthodontic appliances reported noticeably more discomfort than those with aligners, especially while biting and chewing[132]. Furthermore, after the first and second monthly adjustment, patients with fixed appliances reported significantly higher discomfort levels and relied more on painkillers than the aligner group[132].

3. AIMS OF THE STUDY

1. To systematically search the relevant literature in order to synthesize the available evidence on aligner mechanics and tooth loading for all types of orthodontic tooth movement with aligner-type appliances.

2. To determine the accuracy of specific tooth movements with Invisalign and to identify possible reasons for refinement.

3. To systematically review the evidence derived from randomized clinical trials (RCTs) in order to assess if there is any difference in the treatment outcome with aligners compared to fixed appliances for comprehensive orthodontic treatment.

4. To evaluate the changes in the mechanical properties and surface chemistry of aligners treated with cleaning solutions of different composition.

5. To assess the changes in the morphology, roughness and composition of the engaged aligner and composite surfaces in aligner orthodontic treatment with attachments.

4. MATERIALS AND METHODS

4.1 Accuracy of tooth movement with clear aligners

In order to assess the accuracy of tooth movement during orthodontic treatment with aligners (a) a systematic review was designed in order to synthesize the available evidence for all types of orthodontic tooth movement and (b) a retrospective study was conducted in order to determine the accuracy of specific tooth movements with Invisalign and to identify possible reasons for refinement.

4.1.1 Forces and moments generated by aligner-type appliances for orthodontic tooth movement: a systematic review and meta-analysis (I)

A study protocol was specified in advance and registered at PROSPERO (International Prospective Register of Systematic Reviews) no. CRD42019116900.

In vitro/laboratory studies, studies related to the forces/moments exerted by aligners, any clinical trial/retrospective cohort study with at least two groups for comparison. Models for simulated tooth movement with aligners were considered for in-vitro studies. Participants undergoing orthodontic treatment with aligners (irrespective of age), if applicable, would also be considered. All types of aligners used for orthodontic tooth movement were considered eligible, irrespective of material type, thickness and activation. Any type of comparator will be considered, either non-aligner orthodontic devices or different types of aligners (in terms of design, thickness, inclusion of attachments). The primary outcome were forces and/or moments generated, complying with any type of tooth movement produced (i.e., rotation, intrusion, torque). Diagnostic accuracy studies comparing predicted and final tooth movement, before-after studies, finite element studies were excluded.

Detailed electronic search strategies with no language restrictions were developed within seven databases, as of 11 November 2018: Medline via PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), LILACS via BIREME Virtual Health Library. Moreover, unpublished literature was searched in Open Grey, ClinicalTrials. gov (www.clinicaltrials.gov), the National Research Register (www. controlled-trials.com) and Center for Open Science (Open Science Framework), using the terms "aligner" AND "orthodontic". Hand searching of the reference lists of the included studies for full text evaluation was also conducted. Contact with authors of the original studies was implemented to clarify data when needed.

Eligibility assessment was performed independently and in duplicate by two reviewers (AI, DK) not blinded to the identity of the authors of the original studies, their institutions or the results of their research. Titles and abstracts were examined first, followed by full-text evaluation of the potentially included studies. Disagreements were resolved through consultation with a third author (TE), until a consensus was reached.

Data extraction was performed by one reviewer (AI) in pre-piloted forms. The reviewer who was not blinded to author identity or study origin and all information obtained was confirmed by a second (DK). Data derived comprised on details on study design, sample size, interventions/ comparators, tooth type and orthodontic movement examined, outcomes (i.e., forces, moments).

The assessment of the risk of bias was implemented by one author (AI) after calibration with a second (DK) on 15% of the included studies. Entries were confirmed by a second author (DK), and any disagreements were resolved through discussion with a third author (TE). The risk of bias within the included trials was assessed using the Cochrane risk of bias tool in accordance with the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0[133] (a modification of the tool was used to assess risk of bias in in vitro studies).

Clinical heterogeneity of the retrieved and eligible for inclusion studies was assessed through the examination of study settings, eligibility criteria, interventions, experimental conditions prior to intervention assignment, laboratory settings and data collection methods. Statistical heterogeneity was first examined through visual inspection of the confidence intervals (CIs) for the treatment effects on forest plots. A chi-square test was also applied to assess heterogeneity; a p-value below the level of 10% ($p<0.1$) was considered indicative of significant heterogeneity[134]. I test for homogeneity was undertaken as well. Only studies with unclear or low risk of bias overall were intended to be included in the quantitative syntheses. Random effects meta-analyses were conducted as they were considered more appropriate to evince the expected heterogeneity and variations in laboratory settings or simulation conditions. Treatment effects were calculated through pooled standardized mean differences (SMDs) with associated 95% Confidence Intervals (95% CIs) and Prediction Intervals where possible (at least three studies). If more than 10 studies were included in meta-analyses, publication bias was to be explored through standard funnel plots.

Sensitivity analyses were predetermined to explore and isolate the effect of studies with unclear risk of bias on the pooled treatment effect if both low and unclear risk of bias studies were included.

4.1.2 Accuracy of clear aligners: A retrospective study of patients who needed refinement (II)

The study group comprised 20 adult patients (3 men, 17 women) with an average age of 37 years 6 months (range, 18 years 1 month to 79 years 11 months). Crowding ranged from mild (0-3 mm) in 7 subjects to moderate (3-6 mm) in 8 subjects and severe (0.6 mm) in 3 subjects, and 2 patients had minor spacing. Overbites were deep in 13 subjects, but those with normal overbite (4) and anterior open bite (3) were also included. The study protocol was approved by the Institutional Review Board of Saint Louis University (number 27561). All patients received Invisalign treatment in the Department of Orthodontics at Saint Louis University or a private practice under the supervision of the same orthodontist, who is an Invisalign elite provider. The orthodontist planned all the ClinChecks according to his preferences with no restrictions on attachment placement. Aligners were changed every 2 weeks. Average treatment time was 12 months (62.5 months). All patients started treatment in 2014 or later, after Invisalign introduced the SmartTrack material. Inclusion criteria were predefined as follows: (1) all patients received treatment in both arches, (2) all participants successfully completed an initial series of aligners and then had a “refinement” phase, because the treatment goals were not reached, (3) patient charts indicated good compliance with consistent aligner wear, (4) minimal movement of the molars in all 3 planes was planned, and (5) treatment started in 2014 or later. Exclusion criteria were (1) noncompletion of the initial series of aligners, (2) poor compliance, (3) dental restorations before refinement, (4) posterior crossbite, and (5) missing first or second molars.Twenty-nine potential subjects were identified after searching the university's and the private orthodontist's accounts on the Invisalign doctor Web site. After review of patients' charts, 20 patients met the inclusion and exclusion criteria. Despite minimal planned movement of the molars, superimpositions of the initial and achieved models showed that the intermolar width changed by 0.81 mm (60.57 mm) on average.

Records were gathered from the Invisalign doctor Web site. Digital models were exported from ClinCheck as stereolithography files. The initial and final models from the first ClinCheck were labelled as "initial" and "predicted." The initial models of the refinement ClinCheck were labelled as "achieved," since they depicted the actual result after aligner wear[134].

Initial, predicted, and achieved digital models were imported in SlicerCMF (open-source, version 3.1; http://www.slicer.org). The predicted and achieved models were superimposed over the initial ones with regional superimpositions on molars that appeared relatively stable in ClinCheck. The central pits of the first and second molars were traced, and an area of equal radius around them was selected. The regions of interest were limited to the occlusal surfaces if there were attachments (Figure 6), or otherwise the whole crown was selected. Maxillary and mandibular arches were superimposed and measured separately.

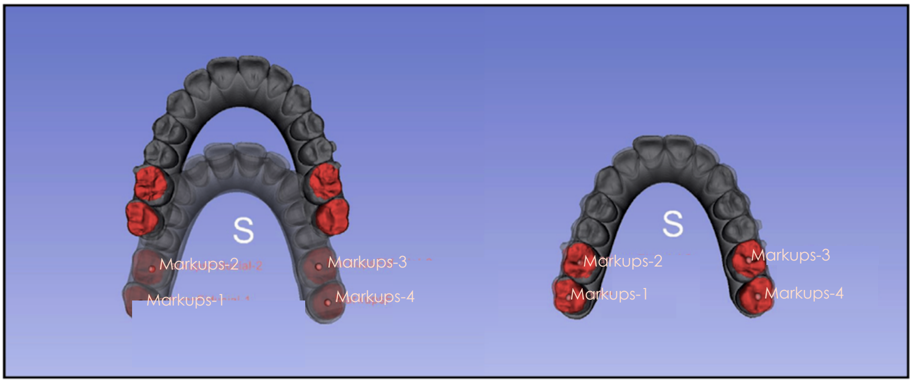

Figure 6. Tracing of central pits and regions of interest (left) and superimposed models (right).

Measurements were made on the initial vs predicted and initial vs achieved models to identify the magnitude and direction of the predicted and achieved movements. Predicted and achieved models were not superimposed on each other. The total number of teeth measured was 398. For every subject, 100 measurements were made (50 predicted and 50 achieved movements) for horizontal movements, vertical movements, rotations, and transverse changes as follows.

1. Horizontal displacements (parallel to the occlusal plane) were measured with the ruler tool at the middle of the incisal edges or cusp tips when the models were viewed directly from the occlusal view (Figure 7).
2. Vertical displacements were measured at the middle of the incisal edges or cusp tips (Figure 7).
3. Intercanine and interpremolar widths were measured at the canine cusp tips and the central grooves or central fossae (depending on the anatomic variation) of the second premolars (Figure 8).
4. Mesiodistal rotations were measured by tracing 2 points on the incisal edges of the incisors: the most mesial and most distal points of the canines and the labial and lingual cusp tips of the premolars. The 2 points were connected on each model with a straight line, and then the angle (yaw) between the lines was measured on the horizontal plane (Figure 9).

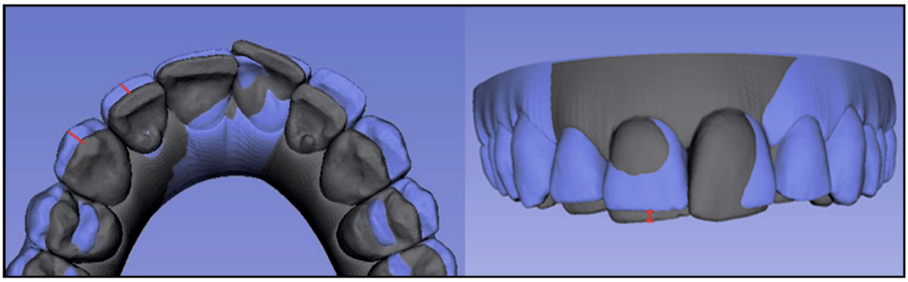

Figure 7. Horizontal and vertical measurements on initial (grey) vs predicted (blue) superimposed models.

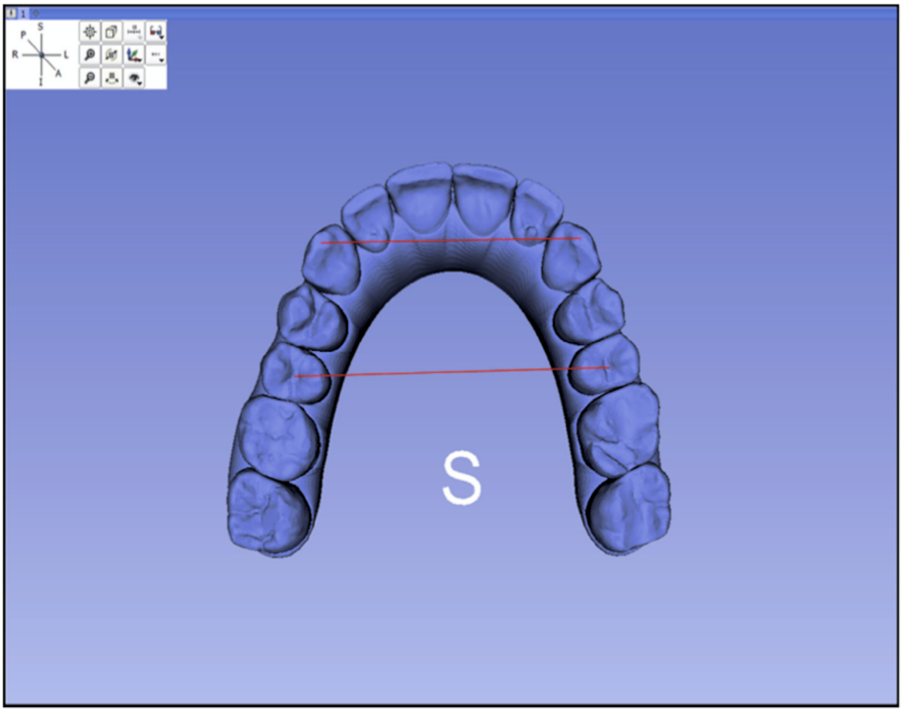

Figure 8. Intercanine and interpremolar widths. The orientation tool on the top left allows for repeatable positioning of the models.

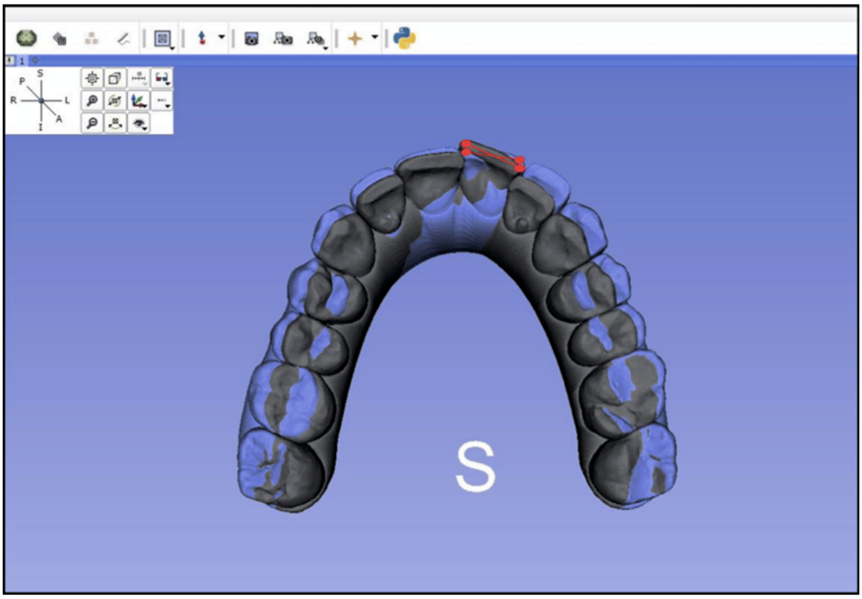

Figure 9. Rotation of a maxillary central incisor.

Statistical analysis

The statistical analysis was performed with SPSS software (version 24.0; IBM, Armonk, NY). Each tooth movement was measured separately. Then the teeth were grouped together as follows to reduce the number of variables: contralateral teeth, first and second premolars, and mandibular central and lateral incisors.

Direction was not considered for horizontal movements and rotations. There was no distinction between labial and lingual displacements as well as clockwise and counter clockwise rotations. However, vertical movement of the incisors was divided into intrusion and extrusion based on the predicted movement. This was considered necessary, since these movements have the opposite effect on overbite, and the literature suggest. that one is more predictable than the other[135].

Descriptive statistics were calculated for each movement. The data distribution was not normal, so the Wilcoxon signed-rank test was used. The level of significance was set at 0.002 after applying the Bonferroni adjustment to control for type I error. The power for the movement with the smallest sample size (n=18) was 95%.

To assess reliability, 1 month after the initial measurements, 10% of the subjects were remeasured by the same examiner. Intraclass correlation coefficients showed high intraobserver reliability, with Cronbach's alpha ranging from .813 to .994 for linear measurements and .832 to .994 for angular measurements.

4.2 Clinical effectiveness of clear aligner treatment

In order to assess the clinical effectiveness of clear aligners when compared to fixed appliances for comprehensive orthodontic treatment a systematic review was designed.

4.2.1 Treatment outcome with orthodontic aligners and fixed appliances: A systematic review with meta-analyses (III)

This review's protocol was made a priori, registered in PROSPERO (CRD42019131589), and all post hoc changes were appropriately noted. This review is conducted and reported according to Cochrane Handbook[133] and PRISMA statement[136], respectively.

According to the Participants-Intervention-Comparison-Outcome-Study design (PICOS) schema and due to the scarcity of RCTs on this subject, included were RCTs and non-randomized clinical studies on human patients of any age, sex, ethnicity, or malocclusion comparing full-arch orthodontic treatment with aligners and fixed appliances. No limitations concerning language, publication year, or status were applied. Due to the scarcity of randomized trials on the subject, non-randomized studies were also included, with the requirement that the populations to be compared were matched regarding baseline malocclusion severity with objective measures like the Peer Assessment Rating (PAR) index[137] or the Discrepancy Index (DI)[138] from the American Board of Orthodontics (ABO). In particular, matching at the design stage was a prerequisite for study inclusion, to eliminate baseline confounding due to potential risk factors that might present a bearing on the outcome of interest. Matching was judged adequate when the Cohen's d for PAR or ABO DI between aligner and fixed appliance group at baseline was up to 0.3. Excluded were animal studies, case reports/series, non-clinical studies, and cross-sectional studies. Excluded were also studies without comprehensive orthodontic treatment, without two distinct treatment groups for aligners/fixed appliances, studies on previously treated patients, and studies without any outcome eligible for this review. The primary outcome for this review was the outcome of comprehensive orthodontic treatment judged with objective and reliable measures like the PAR index and the ABO's Objective Grading System (ABO-OGS) for dental casts and panoramic radiographs[139]. Secondary outcomes included treatment duration, as well as adverse effects like loss of periodontal support, External Apical Root Resorption (EARR), gingival recession, and proclination of the lower incisors during treatment.

Eight electronic databases were searched systematically without any restrictions for publication date, language, or type from inception up to 25 April 2019 (Table 1), while Directory of Open Access Journals (DOAJ), Digital Dissertations, metaRegister of Controlled Trials, WHO, and Google Scholar, as well as the reference/citation lists of eligible articles or existing systematic reviews were manually searched for any additions.

Table 1. Literature search (as of April 7th, 2019) for each database with the corresponding hits.

Database	Search	Limits	Hits
MEDLINE	(orthodon* OR malocclusion* OR "tooth movement" OR "fixed appliances") AND (aligner* OR "clear aligner" OR "clear aligners" OR "ClearCorrect" OR "Invisalign" OR "Orthocaps" OR "TwinAligner")		392
Embase	Same as MEDLINE		60
CDSR	Same as MEDLINE		1
DARE	Same as MEDLINE		0
CENTRAL	Same as MEDLINE		41
Scopus	Same as MEDLINE	Dentistry	260
WOK	Same as MEDLINE	DENTISTRY ORAL SURGERY MEDICINE	200
VHL	Same as MEDLINE		422
Total			1376

CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; DARE, Cochrane Database of Abstracts of Reviews of Effects; VHL, Virtual Health Library; WOK, Web of Knowledge.

Three authors (SNP, DK, AI) screened the titles and/or abstracts of studies retrieved from the searches to identify articles that potentially meet the inclusion criteria, before moving to their full-texts. Any differences between the two reviewers were resolved by discussion with the last author (TE).

Data collection from the identified reports was conducted using predefined and piloted forms covering: (a) study characteristics (design, clinical setting, country), (b) patient characteristics (age, sex), (c) malocclusion and treatment characteristics, (d) appliance type including number of aligners and amount of Interproximal Reduction (IPR) performed, (e) follow-up period, and (f) outcome details. Data were extracted by three authors (SNP, DK, AI) with the same way to resolve discrepancies as above.

The risk of bias of included studies was assessed according to Cochrane guidelines with the RoB 2.0 tool for randomized trials[140] and the ROBINS-I ('Risk Of Bias In Non-randomised Studies of Interventions') tool for non-randomized studies[141]. Assessment of the risk of bias within individual trials was likewise performed independently by three authors (SNP, DK, AI), with the same way to resolve discrepancies consulting the last author (TE).

An effort was made to include all existing trials in the analysis; where data were missing, they were calculated by ourselves, requested from the authors or calculated from graphs. As the outcome of orthodontic treatment is bound to be affected by patient and treatment-related characteristics, a random- effects model was deemed appropriate to calculate the average distribution of true effects, based on clinical and statistical reasoning[142], and a restricted maximum likelihood random-effects model was used according to recent guidance[143]. Mean differences (MDs) for continuous outcomes and relative risks (RRs) for binary outcomes and their corresponding 95% confidence intervals (CIs) were calculated as effect sizes. Statistically significant RRs were translated into Numbers Needed to Treat (NNTs) to gauge their clinical relevance.

The extent and impact of between-study heterogeneity was assessed by inspecting the forest plots and by calculating the τ^2 (absolute heterogeneity) or the I^2 statistics (relative heterogeneity). I^2 defines the proportion of total variability in the result explained by heterogeneity, and not chance, and we considered arbitrarily I^2 over 75% to represent considerable heterogeneity, while also considering the heterogeneity's direction (localization on the forest plot) and uncertainty intervals around heterogeneity estimates[144]. Ninety-five percent predictive intervals were calculated for meta-analyses of at least three trials to incorporate existing heterogeneity and provide a range of possible effects for a future clinical setting, which are crucial for the correct interpretation of random-effects meta-analyses[145].

Possible sources of heterogeneity were a priori planned to be sought through subgroup analyses and random-effects meta-regression in meta-analyses of at least five trials but could ultimately not be performed. Likewise, reporting biases were planned but ultimately not assessed, due to the limited number of meta-analyzed trials. The overall quality of meta-evidence (i.e., the strength of clinical recommendations) was rated using the Grades of Recommendations, Assessment, Development and Evaluation (GRADE) approach[146] following recent guidance on combining randomized with non- randomized studies[147] and summary of findings tables were constructed using the improved format proposed by Carrasco-Labra et al.[148]. The minimal clinically important, large and very large effects were defined as half, one and two standard deviations of the post-treatment response (for continuous outcomes) and RRs of 1.5, 2.0, and 5.0 (for binary outcomes)[149,150]. The produced forest plots were augmented with contours denoting the magnitude of the observed effects to assess heterogeneity, clinical relevance, and imprecision[151].

Robustness of the results was planned a priori to be checked with sensitivity analyses based on (a) inclusion/exclusion of non-randomized studies, (b) inclusion/exclusion of trials with methodological shortcomings, and (c) improvement of the GRADE classification. In the end, only one sensitivity analysis excluding non-randomized studies could be conducted. All analyses were run in Stata version 14.0 (StataCorp LP, College Station, TX) by one author (SNP) and the dataset was openly provided[152]. All p-values were two-sided with $\alpha=5\%$, except for the test of between-studies or between-subgroups heterogeneity where α-value was set as 10%[153].

4.3. Effects of cleansers and attachments on the surface topography and structure of clear aligners

In order to evaluate the changes on the surface topography and structure of clear aligners two in- vitro studies were designed. The first one assessed the mechanical properties and surface chemistry of aligners treated with cleaning solutions of different composition and the second the changes in the morphology, roughness and composition of the engaged aligner and composite surfaces in aligner orthodontic treatment with attachments.

4.3.1 Effect of cleansers on the composition and mechanical properties of orthodontic aligners in vitro (IV)

The aligners and the cleaning agents tested are presented in Table 2. Forty unused upper aligners of Clear Aligners (C) and Invisalign (I) aligners were obtained from an orthodontic practice and classified into four groups of ten specimens each per material. The cleansing solutions of Retainer Brite (RB) and Retainer Cleaner (RC) were prepared by dissolving each tablet in 150 ml of tap water, whereas for Steraligner (ST) 15 ml of the liquid was mixed with 135ml of tap water.

Table 2. The aligner materials and the cleaning agents used in the study

Product/code	Composition*	Manufacturer
Aligners		
CA Clear Aligner/C	Polyethylene terephthalate glycol	Scheu-Dental GmbH, Iserlohn, Germany
Invisalign/I	Polyester – urethane.	Align Technology, San Jose, CA, USA
Cleaning agents		
Retainer Brite/RB	Potassium peroxymonosulfate, Sodium perborate monohydrate, Sodium bicarbonate, Sodium sulfate, Sodium carbonate, Pentasodium triphosphate, Corn syrup solids, Sodium lauryl sulfoacetate, PEG-180, Flavor, Magnesium stearate, Tetrasodium EDTA, Citric acid, FD&C Blue #1, FD&C Blue #2	Dentsply Sirona, Sarasota, FL, USA
Retainer Cleaner/RC	Potassium peroxymonosulfate, Sodium percarbonate, PEG-150, Peppermint oil, Indigo, Sodium benzonate, Sodium bicarbonate, Tetrasodium EDTA, Sodium lauryl sulfate Surfactant,	Fancymay, Greenland, (Amazon Associate) TJA Health LLC, Joliet, IL, USA
Steraligner/ST	Polyrsorbate 20, Sodium pyrophosphate, Tetrapotassium salt (undefined), Essential oil complex, Sodium gluconate, 2-propanol, Disodium EDTA, Sodium benzo- nate, Sodium bicarbonate, FD&C Blue #1	TJA Health LLC, Joliet, IL, USA

Aligners designated for (RB) and (RC) treatment groups were immersed in individual caps with the cleaning agents for 15 min, whereas a 5-min immersion period was used for the (ST) group, according to the manufacturer's instructions. After each cleansing cycle, the aligners were rinsed thoroughly with tap water and then stored in dry conditions. This procedure was repeated 14 times, once per day for a two-week period, corresponding to a daily cleaning during the instructed in-service function of each appliance. Aligners non-immersed in the cleaning solutions were used as control (CO).

The pH of 150 ml freshly made cleaning solutions was measured by a calibrated pH meter (P 903, Consort NV, Turnhout, Belgium) employing a standard liquid probe. Measurements were performed two minutes after mixing in triplicate and the values were averaged.

Ten upper first molars from different appliances of each testing group (RB, RC, ST, CO) per aligner type (C, I) were sectioned. The specimens were embedded in self-curing acrylic resin (Verso Cit-2, Struers, Ballerup, Denmark), with their occlusal surfaces parallel to the horizontal plane. The samples were ground up to 4000 grit-size SiC papers under water cooling, and polished with a water-based diamond suspension (Nap R1 DiaPro, Struers) in a grinding/polishing machine (Dap-V, Struers). Then, the specimens were subjected to Instrumented Indentation Testing (IIT), employing a universal hardness testing machine (ZHU0.2/Z2.5, Zwick Roell, Ulm, Germany) with a

Vickers indenter for determination of the following mechanical properties: the Martens Hardness (HM), indentation modulus (E_{IT}), elastic index (n_{IT}) which is indicative for the brittleness of the material, and the indentation relaxation (R_{IT}). Two different loading regimes were applied. The HM, E_{IT} and n_{IT} were acquired from force–indentation depth curves applying a maximum load of 2.9 N for 2 s contact time. The R_{IT} (monitoring the load level, while maintaining a constant contact area between the indenter and the material) was measured employing a tetragonal force pulse where a constant indentation depth was applied for 60 s and the R_{IT} was measured by recording the force decrease between the start and the end of the constant indentation depth period. All mechanical properties were measured according to the equations provided by the international standard ISO14577-1, 2002[154].

Another series of specimens was prepared by sectioning as above. Intact occlusal specimen surfaces were analyzed by Attenuated Total Reflectance Fourier Transform Infrared Spectrometry (ATR-FTIR), employing a spectrometer (Spectrum GX, PerkinElmer, Buckinghamshire, Bacon, UK) equipped with an ATR accessory (Golden Gate, Specac, Orpington, Kent, UK) with a diamond type III crystal (2×2 mm) and a sapphire anvil. Spectra were acquired after under the following conditions: 4000– 650 cm^{-1} wavenumber range, 4 cm^{-1} resolution, 20 scans co-addition, 2μm depth of analysis at 1000 cm^{-1}. The spectra of treated specimens were compared with the controls to identify changes in peak positions indicating the presence of new chemical groups. Furthermore, to verify the H-bonding status of the polyester backbone, the 1800–1650 cm^{-1} wavenumber range of all spectra was subjected to curve-fitting analysis (Gaussian area mode) employing PeakFit v.4.12 software (Seasolve, Framingham, MA, USA).

Statistical analysis

The results of pH and mechanical properties were initially tested for normality (Shapiro-Wilk) and homoscedasticity (Brown-Forsyth) tests. For normally distributed data, comparisons were carried out by one-way ANOVA, whereas for data failed to pass normality tests, the nonparametric one-way ANOVA on Ranks (Kruskal-Wallis) test was used. In all cases, Tukey post hoc multiple comparison tests were used to allocate differences among groups. The level of statistical significance for all tests was set at a=0.05. Statistical analysis was carried out employing SigmaPlot v 14 software (Systat Software Inc, San Jose, CA, USA).

4.3.2 Surface alterations of resin composite attachments induced by orthodontic aligners: An in-vitro study (unpublished data)

Zirconia CAD/CAM full arch frames (n=20) and corresponding thermoformed polyethylene terepthalate glycol (PET-G) aligners (Clear Aligners, Scheu-Dental, Iserlohn, Germany) with standardized spaces for the attachments (rectangular and ellipsoid) were manufactured (Figure 10). On each frame eight resin attachments were bonded on the buccal surfaces of central and lateral incisors, canines and first premolars. The attachments were bonded as follows: The zirconia frame surfaces were grit-blasted with 50 μm alumina employing an intraoral sandblasting device (Microetcher IIA, Danville Materials) operated for 5 s at 2.3 bar air pressure (0.23 MPa, 0.47 L/s flow rate), 5 mm distance and 90^{o} angle. The grit-blasted surfaces were then treated with a universal primer (G-Multi Primer, GC Europe NV, Leuven, Belgium) according to the manufacturer's instructions. Half of the attachment templates were filled with a sculptable universal composite restorative material (Group I, Tetric Evo Ceram, A2 shade, Ivoclar Vivadent, Shaan, Liechtenstein) whereas for the rest a low shrinkage universal flowable resin composite (Group II, Tetric Power Flow, A2 shade, Ivoclar Vivadent) was employed. Attachment templates were then pressed against the sandblasted zirconia frames and light-cured for 20 s (each attachment) with a LED curing unit (Bluephase G20i, Ivoclar Vivadent) emitting 1600 mW/cm^2 intensity in standard mode. After excess removal, the frames with the aligners were immersed in 50 mL of distilled water and stored in sealed vials at 37^{o}C under dark conditions. Eight aligners of each group were removed and re-seated to the zirconia frames 4 times per day for a 7-day immersion period, whereas the rest remained intact. After the testing period, the aligners were removed and the corresponding attachment surfaces being in contact with the aligner, were studied for morphological features, roughness and composition.

The attachments were examined under a stereomicroscope (M80, Leica) at 7.5 or 25× magnification under reflected light.

Figure 10. Zirconia CAD/CAM full arch frames.

All the bonded composite attachments were examined by an optical profiler (Wyko NT1100, Veeco, Tuscon, AZ, USA) employing a Mirau lens at 10× magnificaton (462.2 × 607.5 μm² analysis area), vertical scanning mode, 2% modulation and tilt correction. The 3D-roughness parameters determined were the Sa, Sq, Sz (amplitude), Sdr, Sds, Ssc (hybrid), and Sc, Sv (functional). Sa is the arithmetic average of the absolute values of the surface height deviations measured from the best fitting plane; Sz is the 10 point height over the surface, representing the average distance between the five highest peaks and five lowest valleys; Sdr is the developed area due to the surface texture versus an ideal plane area ratio; Sds is the summit density defining the number of peaks per unit area of the surface, Ssc is the mean summit curvature, indicating the shape and size of the higher areas of a surface Sc (core void volume) is the volume supported by the surface from 10–80% of the bearing ratio and Sv (surface void volume) is the volume the surface would support from 80% to 100% of the bearing ratio.

The molecular composition of representative abraded composite surfaces and their controls was evaluated by atenuated total reflection FTIR spectroscopy (ATR-FTIR). Randomly selected specimens (n=10/product) were carefully debonded from the zirconia frames using a straight cutter plier with a torque motion, air-dried and the central regions facing the aligner were pressed via a sapphire anvil against a single-reflection diamond type IIa element (2×2 mm) of an ATR accessory (ZnSe lenses, 45^{o} incidence angle; Golden-Gate MKII, Specac, Oprington, Kent, UK) attached to an FTIR spectrometer (Spectrum GX, Perkin-Elmer, Buckinghamshire, Bacon, UK). Spectra were recorded under the following conditions: 4000-650 cm^{-1} wavenumber range, 4 cm^{-1} resolution, 20 scans co-addition and ~2 μm sampling depth at 1000 cm^{-1}. Furthermore, the degree of C=C bond conversion (DC%) of the attachments was measured employing spectra of unset restorative materials, obtained under the same conditions, as reference. The DC% was calculated based on the two-band technique according to the equation:

$$DC\% = 100 \times [1 \times (Ap_{(C=C)} \times Am_{(Ar)} / Am_{(C=C)} \times Ap_{(R)}]$$

where, A is the net peak absorbance height of the set (p) and unset (m) peaks of the methacrylate C=C bond stretching vibrations at 1636 cm^{-1} (analytical band; changes after photopolymerization) and R the aromatic (Ar) stretching vibrations at 1608 cm^{-1} (reference band; not affected by photo polymerization).

Statistical analysis

The roughness parameters and degree of C=C conversion values were tested for normality (Shapiro-Wilk test) and homoscedasticity (Brown-Forsythe test). For each property comparisons were made between controls (intact aligners) vs aligners after removal and re-seating. Moreover, comparisons between materials (conventional vs flowable composites) were registered. The level of statistical significance was pre-specified at a= 0.05. All statistical analyses were performed with SigmaPlot v.14 software (Systat Software Inc., San Jose, CA, USA).

5. RESULTS

5.1 Accuracy of tooth movement with clear aligners

5.1.1 Forces and moments generated by aligner-type appliances for orthodontic tooth movement: a systematic review and meta-analysis (I)

A total number of 447 studies were retrieved and the aforementioned inclusion criteria were applied. The flow chart describing the study identification process is presented in Figure 11. After abstract- and full-text reading stage, 13 studies were considered eligible for this review (Table 3). All 13 studies were in vitro studies.

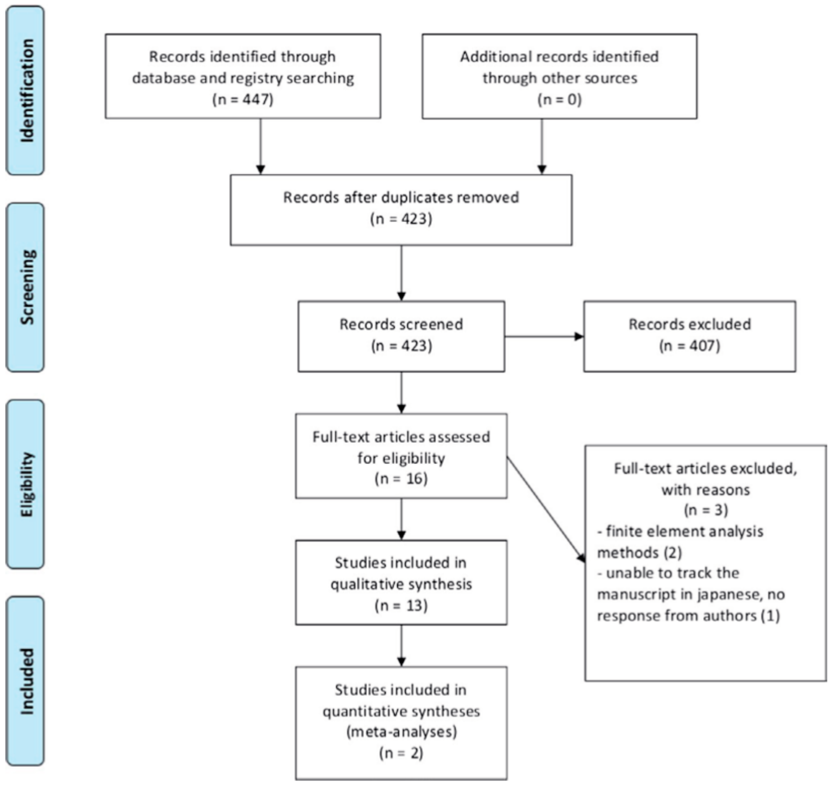

Figure 11. Flow diagram of article retrieval

Table 3. Characteristics of included studies (n=13)

id	Author and Year of Publication	Study design	Sample size/teeth type	Groups under comparison	Interventions	Outcomes
1	Brockmeyer et al (2017)	in vitro	Total n=45 aligners, same thickness 1mm Biolon uncut n=5, z11 n=5, z12-21 n=5 IdealClear uncut n=5, z11 n=5, z12-21 n=5 upper central incisor	Material vs cut, deflection distance vs material, deflection distance vs cut	Thermoplastic aligners modified by incisal cuts	Horizontal force component magnitude, vertical force component magnitude in labial and palatal translation of upper central incisors
2	Elkholy et al (2015)	in vitro	Total n=27 aligners Duran 0.5mm (n=3), 0.625mm (n=3), 0.75mm (n=3) Erkodur 0.5mm (n=3), 0.6mm (n=3), 0.8mm (n=3) Track-A 0.5mm (n=3), 0.63mm (n=3), 0.8mm (n=3) upper central incisors	Forces delivered aligner/ thickness	Different aligner thickness n material Duran 0.5mm (n=3), 0.625mm (n=3), 0.75mm (n=3) Erkodur 0.5mm (n=3), 0.6mm (n=3), 0.8mm (n=3) Track-A 0.5mm (n=3), 0.63mm (n=3), 0.8mm (n=3)	Forced and moments magnitude to upper central incisor for labial and pala- tal translation
3	Elkholy et al (2016)	in vitro	Total n=15 Duran 0.3mm (n=3) 0.4mm (n=3) 0.5 mm (n = 3) 0.625 mm (n = 3) 0.75 (n = 3) upper central incisors	Forces delivered aligner/ thickness	Reduced thickness aligners Duran 0.3mm (n = 3), 0.4mm (n = 3), 0.5mm (n = 3) 0.625mm (n=3) 0.75mm (n=3)	Forces and moments delivered during labiopalatal movement of upper central incisor
4	Elkholy et al (2017) (AJODO)	in vitro	Total n = 15 Duran 0.5 mm (n = 3), 0.625 mm (n = 3), 0.75 mm (n = 3) vs 0.3 mm (n = 3), 0.4 mm (n = 3) upper central incisors	Forces applied by 0.3/0.4 mm aligners vs conventional >0.5 mm	Reduced thickness aligners 0.4, 0.3mm Duran 0.5mm (n=3), 0.625mm (n=3), 0.75mm (n=3) vs 0.3mm (n=3), 0.4mm (n=3)	Forces and moments delivered during mesiodistal derotation of upper central incisor
5	Elkholy et al (2017) (J Orofac Orthop)	in vitro	Total n=9 Duran 0.5mm (n=3), 0.625mm (n=3), 0.75 mm (n = 3) mandibular canine	Forces delivered aligner/ thickness	Duran 0.5 mm (n = 3), 0.625 mm (n = 3), 0.75 mm (n = 3)	F orces and moments delivered during mesial and distal derotation of mandibular canine
6	Gao et al (2017)	in vitro	Total n = 27*2 = 54 Duran 0.5 mm/0-1 width n = 3 Duran 0.5 mm/3-4 width n = 3 Duran 0.5 mm/6-7 width n = 3 Duran 0.625 mm/0-1 width n = 3 Duran 0.625 mm/3-4 width n = 3 Duran 0.625 mm/6-7 width n = 3 Duran 0.75 mm/0-1 width n = 3 Duran 0.75 mm/3-4 width n = 3 Duran 0.75 mm/6-7 width n = 3 Upper central incisor	Edge width comparison/ aligner thickness	Different aligner thickness width Duran 0.5 mm/0-1 width n = 3 Duran 0.5 mm/3-4 width n = 3 Duran 0.5 mm/6-7 width n = 3 Duran 0.625 mm/0-1 width n = 3 Duran 0.625 mm/3-4 width n = 3 Duran 0.625 mm/6-7 width n = 3 Duran 0.75 mm/0-1 width n = 3 Duran 0.75 mm/3-4 width n = 3 Duran 0.75 mm/6-7 width n = 3	Forces and moments delivered during maxillary central incisor palatal tipping and intrusion
7	Hahn et al (2010) (Angle)	in vitro	n=15 Ideal Clear 1 mm n = 5 Erkodur 1 mm n = 5 Biolon 1 mm n = 5 Upper central incisor	Forces delivered aligner material	Different aligner material	Force system and moments produced by 3 different types of plastic aligners during rotation
8	Hahn et al (2010) (EJO)	in vitro	n=15 Ideal Clear 1 mm n = 5 Erkodur 1 mm n = 5 Biolon 1 mm n = 5 Upper central	Forces delivered aligner material	Different aligner material	Force system and moments produced by 3 different types of plastic aligners during torque
9	Hahn et al (2011)	in vitro	n=20 Biolon 0.75 mm n = 5 Biolon 1 mm n = 5 Erkodur 0.8 mm n = 5 Erkodur 1 mm n = 5 upper central	Forces delivered mate- rial/with and without simulated occlusal forces	Different aligner material + oc- clusal forces	Forces produced by two different types of aligners with and without simulated occlusal forces during rotation of upper central incisors

10	Li et al (2016)	in vitro	n = 5, Erkodur 1 mm activation 0.2 mm n=1 activation 0.3 mm n = 1 activation 0.4 mm n = 1 activation 0.5 mm n = 1 activation 0.6 mm n = 1 upper central	Forces delivered be- tween various amounts of activation aligners	Aligners with various amounts of activation	Forces delivered between various amounts of activation aligners and attenuation during lingual bodily move- ment of upper central incisor
11	Liu et al (2018)	in vitro	n = 55, Duran 0.8 mm thickness G0 control n = 5 G1 intrude mand canines by 0.2 mm n = 5 G2 intrude 4 mand incisors by 0.2 mm n=5 G3 intrude canines and inc by 0.2 mm n=5 G4 intrude can 0.1 mm, lat inc 0.15 mm, centr inc 0.2 mm plus attachments on 1st and 2nd premolars and 1st molars	G0, G1, G2, G3, G4	Aligners with different activation	Forces delivered between various types/amount of aligner activation dur- ing intrusion of lower anterior
12	Mencattelli et al (2015)	in vitro	All in, Micerium n = 3 -aligner with no forces n = 1 -aligner without divot n = 1 -aligner with divot n = 1 maxillary central incisor	With divot/without divot	Aligner with divot	Forces delivered from aligner with divot during rotation
13	Simon (2014)	in vitro	n = 970 aligners (60 series/30 patients) Invisalign incisor torque*, n = 10 patients (split mouth torque <10o + attachment) premolar derotation*, n = 10 patients (split mouth derotation <10o + attachment) molar distalization*, n = 10 patients (split mouth distalization <1.5 mm + attach- ment)*20 tooth movements (2 per patient)	With/without attach- ments in specific movements: torque, derotation, distalization	With/without attachments	Initial force systems that are delivered by an individual aligner, force systems generated by a series of aligners, influ- ence of auxiliaries (attachments, power ridges) on the force transfer

All included studies were published between 2010 and 2018 and reviewed 6 different aligner materials (Biolon, Erkodur, Ideal Clear, Duran, All-In, Invisalign) with foil thickness from 0.3 to 1 mm. Six distinctive types of tooth movement were described with the use of the aforementioned aligner combination thickness (Table 3).

The risk of bias of the thirteen included in vitro studies was assessed using a modified version of the Cochrane risk of bias tool[133] (Figure 12). Eleven studies[15,17,19,28,155-161] stated clearly the experimental conditions which were comparable between groups. Blinding of the assessors was considered unclear. Losses or non-inclusion of specimens were not reported thus no attrition bias was detected and there was no evidence of selective outcome reporting. Based on the aforementioned points these studies were classified as unclear risk of bias. In two studies[162,163], blinding if the assessors was not feasible due to the nature of the interventions thus, these studies were rated as high risk of bias.

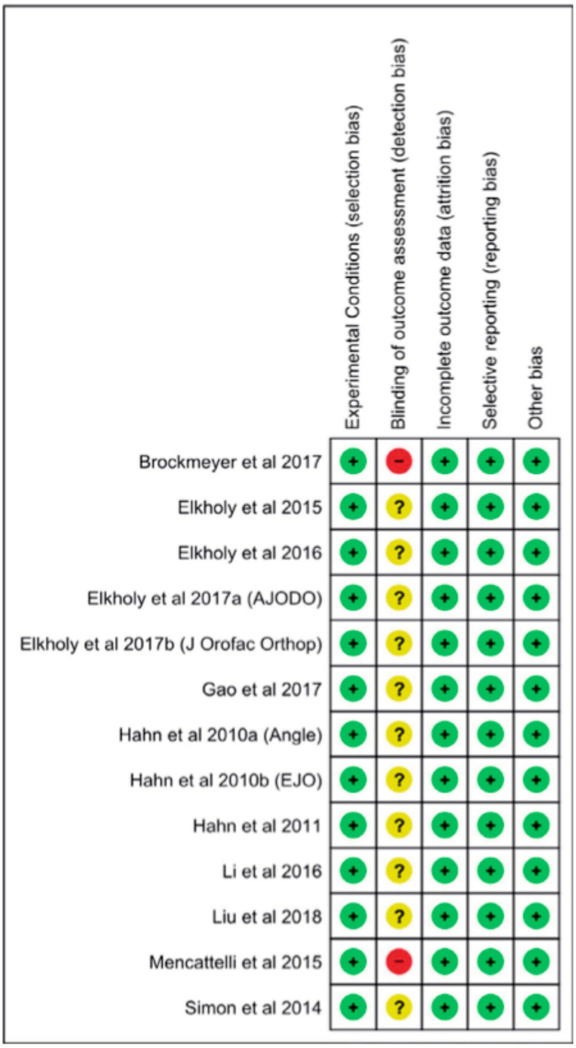

Figure 12. Risk of bias summary outlining judgement of risk of bias items for each of the included studies. The plus sign indicates low risk of bias; the circle with question mark indicates unclear risk of bias; the minus sign indicates high risk of bias

Effects of interventions

Quantitative synthesis of included studies

Quantitative analysis was only feasible between two of the included studies[15,156], and pertained to palatal tipping movement of maxillary central incisor, generated by PET-G aligners trimmed to a gingival edge width of 3-4 mm. There was no difference between any of the retrieved aligner thickness comparisons with regard to moment to force (M/F) ratio. More specifically, for aligner thickness of 0.5 mm compared to that of 0.75 mm the pooled estimate was a standardized mean difference (SMD) of −3.33 (95% CI: −9.63, 2.96; p-value = 0.30; I^2 = 82.0%; Figure 13). Accordingly, no differences to M/F ratio were detected for comparisons between 0.5- and 0.625-mm thickness (SMD = −0.43; 95% CI: −4.16, 3.29; p-value = 0.82; I^2 = 84.1%; Figure 14), or 0.625 to 0.75 mm (SMD = −0.98; 95% CI: −7.41, 5.46; p-value = 0.77; I^2 = 89.9%; Figure 15), as well.

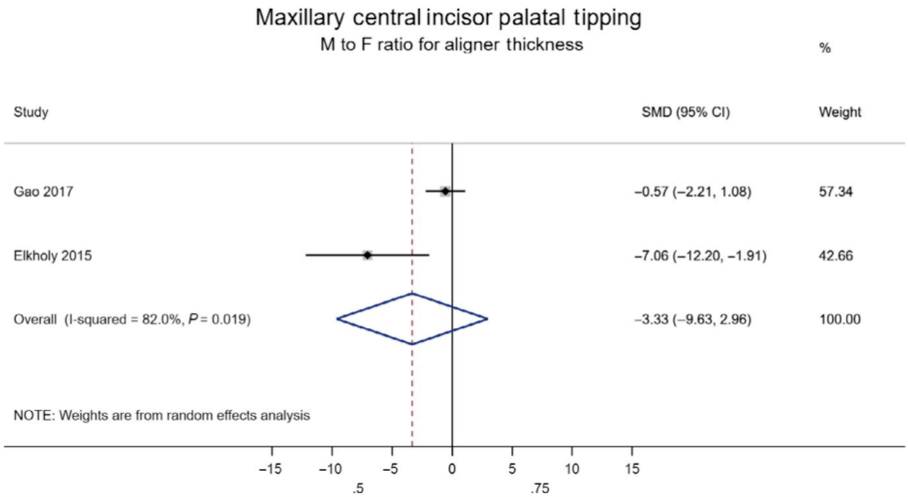

Figure 13. Random effects meta-analysis for the effect of aligner thickness on moment to force (M/F) ratio, for palatal tipping of the upper central incisor (aligner thickness: 0.5 mm vs 0.75 mm)

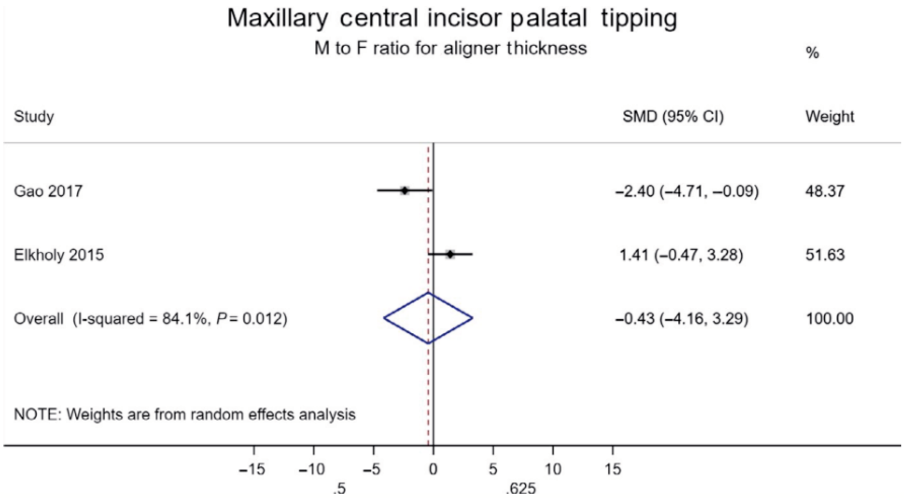

Figure 14. Random effects meta-analysis for the effect of aligner thickness on moment to force (M/F) ratio, for palatal tipping of the upper central incisor (aligner thickness: 0.5 mm vs 0.625 mm)

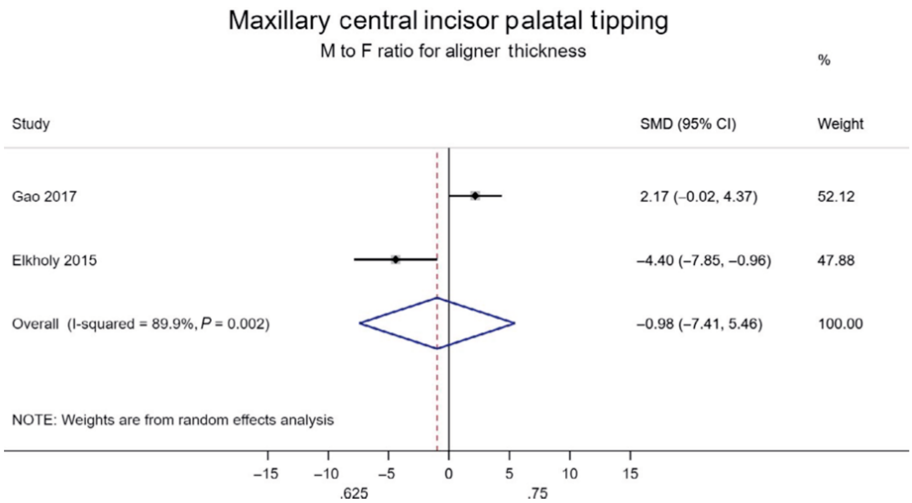

Figure 15. Random effects meta-analysis for the effect of aligner thickness on moment to force (M/F) ratio, for palatal tipping of the upper central incisor (aligner thickness: 0.625 mm vs 0.75 mm)

Qualitative synthesis of included studies

The included studies were examined from three different perspectives regarding aligner thickness, generated tooth movement and aligner material. This arbitrary categorization was implemented simply to facilitate data comprehension.

Aligner thickness

The thickness of plastic foil used for thermoforming PET-G aligners ranged from 0.3 to 1 mm. The forces generated by the thinnest commercially available aligners of 0.5 mm resulted in significant overloading of the periodontal structures[155]. When PET-G aligners of reduced thickness, namely of 0.4 and 0.3 mm were used, the aforementioned forces were decreased by 35% and 71%, respectively[155]. It has been reported that aligner thickness of 0.3 mm, may reduce rotational stiffness by 76%[157]. Despite the fact that 0.3 mm PET-G aligners seem to exert ideal forces, they are considered unsuitable for clinical use due to deformation[155,157]. Thus, a sequence of aligners including 0.4, 0.5, 0.75 mm has been proposed in order to achieve low initial stiffness combined with a steady load[155,157,158]. As for 0.625 and 0.75 mm PET-G foils, findings indicate that both presented similar mechanical behaviour with respect to rotational moments during mandibular canine and maxillary central incisor rotation[157,158] as well as labio-lingual tipping and bodily movement[15,155,156]. Three studies[19,17,159] examined the behaviour of 1mm PET-G aligners and concluded that forces and moments generated were higher than those recommended. Finally, forces applied by 0.7mm Invisalign system aligners have been reported to lie within the range of acceptable orthodontic forces[28].

Type of tooth movement

Tipping of upper central incisors[162] and lower canine intrusion[161] is feasible with the use of PET-G aligners. On the contrary, three studies[155,159,160] indicated that bodily movement and torque are the most demanding movements to achieve since plain aligners without modifications cannot establish the force couple required. Upper incisor rotation movement with aligners has been frequently coupled with an intrusive force, which may present an increase in magnitude when combined with simulated occlusal forces[17,19,157]. Hahn et al[17], found that only a slight activation of ±0.17 mm or 0.5° per step during rotation could produce ideal forces which have been estimated to range between 0.35 and 0.6 N[164]. Finally, Simon et al stated that Invisalign aligners bear the potential to deliver force levels of such magnitude, which may produce premolar derotation, bodily movement, molar distalization and torque when combined with appropriate attachment setups[28].

Aligner material

All four studies[17,19,159,162] comparing different PET-G aligner materials of 1 mm thickness reported that aligners vacuum-formed with Biolon (Dreve Dentamid GmbH, Unna, Germany) delivered the highest forces and moments ranging from 1.15 to 6.19 N[159,162] during tipping and 35.3-71.8 Nmm[17,19] during rotation, depending on the activation magnitude. The only exception was observed during rotation at low rotation range of ±0.17 mm were the Ideal Clear appliance (Dentsply GAC, Gräfelfing, Germany) exerted the highest values (18.3-20.2 Nmm)[17]. Finally, the lowest forces and rotational moments were reported for Erkodur (Erkodent Erich Kopp GmbH, Pfalzgrafenweiler, Germany) at all activation ranges[17,19,159,162].

Finally, three studies[28,162,163] reported the importance of aligner modifications in order to achieve the desired rotation. The use of divots corresponding to the tooth to be treated was found to increase rotational forces by 58%[163], whereas the placement of attachments in teeth with short crowns and few undercuts facilitated as well the delivery of the necessary force system[162].

Exploring for publication bias either statistically or graphically was not possible as no more than 3 studies contributed to individual quantitative syntheses.

5.1.2 Accuracy of clear aligners: A retrospective study of patients who needed refinement (II)

Descriptive statistics of the predicted and achieved tooth movements are presented in Table 4.

Table 4. Descriptive statistics

		Predicted			Achieved		
Movement	n	Mean	Median	SD	Mean	Median	SD
Maxillary central incisor horizontal (mm)	40	1.14	1.00	0.98	0.90	0.65	0.82
Maxillary lateral incisors horizontal (mm)	40	1.14	0.80	0.88	0.88	0.60	0.77
Maxillary canines horizontal (mm)	40	1.11	1.15	0.76	0.84	0.80	0.65
Maxillary central incisors intrusion (mm)	22	0.99	1.00	0.49	-0.37	-0.25	0.75
Maxillary central incisor extrusion (mm)	18	1.28	1.35	0.79	1.64	1.80	1.02
Maxillary lateral incisors intrusion (mm)	18	0.70	0.50	0.64	-0.22	-0.40	0.76
Maxillary lateral incisors extrusion (mm)	22	0.97	0.90	0.72	1.24	0.95	0.86
Maxillary canines vertical (mm)	40	0.61	0.30	0.71	0.70	0.50	0.71
Maxillary intercanine width change (mm)	20	2.09	2.05	1.20	1.60	1.45	1.06
Maxillary interpremolar width change (mm)	20	1.49	1.45	1.08	1.16	1.10	0.86
Maxillary central incisors rotation (º)	40	5.45	4.40	4.22	3.12	2.25	3.01
Maxillary lateral incisors rotation (º)	40	9.16	6.50	8.04	6.06	3.75	6.56
Maxillary canine rotation (º)	40	8.83	6.50	7.95	5.00	2.50	5.42
Maxillary premolars rotation (º)	79	4.07	3.40	3.59	3.02	2.00	2.89
Mandibular incisors horizontal (mm)	80	1.13	1.00	0.80	1.11	1.00	0.82
Mandibular canines horizontal (mm)	40	1.21	1.00	1.03	1.03	0.80	0.87
Mandibular incisors intrusion (mm)	64	1.33	1.10	0.85	0.34	0.30	0.70
Mandibular incisors extrusion (mm)	16	0.67	0.25	0.86	0.58	0.40	0.44
Mandibular canines vertical (mm)	40	0.86	0.70	0.62	0.44	0.40	0.40
Mandibular first premolars vertical (mm)	40	0.37	0.20	0.42	0.38	0.30	0.30
Mandibular intercanine width change (mm)	20	1.90	1.85	1.21	1.85	1.65	1.16
Mandibular interpremolar width change (mm)	20	1.76	1.25	1.70	1.67	1.50	1.56
Mandibular incisors rotation (º)	80	10.83	7.75	8.99	8.19	5.95	7.37
Mandibular canine rotation (º)	40	13.19	11.40	10.69	9.34	7.95	7.40
Mandibular premolars rotation (º)	79	7.76	5.90	6.42	5.05	3.90	4.54

A negative sign indicates that the opposite movement was observed (extrusion).

Wilcoxon signed-rank tests between predicted and achieved measurements were performed to assess the accuracy of each movement. The results are given in Table 5. A negative value indicates that the achieved values were greater than the predicted ones.

Table 5. Wilcoxon signed-rank test between predicted and achieved movements.

Movement	Median predicted	Median Difference (predicted - achieved)	P value
Maxillary central incisor horizontal (mm)	1.00	0.25	*
Maxillary lateral incisors horizontal (mm)	0.80	0.25	NS
Maxillary canines horizontal (mm)	1.15	0.20	*
Maxillary central incisors intrusion (mm)	1.00	1.50	*
Maxillary central incisor extrusion (mm)	1.35	-0.30	NS
Maxillary lateral incisors intrusion (mm)	0.50	1.10	*
Maxillary lateral incisors extrusion (mm)	0.90	-0.25	NS
Maxillary canines vertical (mm)	0.30	-0.10	NS
Maxillary intercanine width (mm)	2.05	0.45	*
Maxillary interpremolar width (mm)	1.45	0.25	NS
Maxillary central incisors rotation (°)	4.40	2.00	*
Maxillary lateral incisors rotation (°)	6.50	1.85	*
Maxillary canine rotation (°)	6.50	3.05	*
Maxillary premolars rotation (°)	3.40	0.90	*
Mandibular incisors horizontal (mm)	1.00	0.00	NS
Mandibular canines horizontal (mm)	1.00	0.20	NS
Mandibular incisors intrusion (mm)	1.10	0.80	*
Mandibular incisors extrusion (mm)	0.25	-0.30	NS
Mandibular canines vertical (mm)	0.70	0.30	*
Mandibular premolars vertical (mm)	0.20	0.00	NS
Mandibular intercanine width (mm)	1.85	-0.10	NS
Mandibular interpremolar width (mm)	1.25	0.00	NS
Mandibular incisors rotation (°)	7.75	1.85	*
Mandibular canine rotation (°)	11.40	2.45	*
Mandibular premolar rotation (°)	5.90	1.90	*

A negative sign indicates that the achieved value was greater than the predicted one.
NS, Not significant
*Statistically significant difference ($P<0.002$)

Overall, horizontal movements of all incisors seemed to be accurate, with differences either small (0.20- 0.25 mm) or insignificant. Extrusion of incisors also appeared to be accurate, since no statistically significant differences were observed. Conversely, intrusion of incisors was the most inaccurate of all linear movements. The maxillary central incisors had the greatest difference of 1.5 mm ($p<0.002$).

The discrepancy for horizontal movement of the canines was significant in the maxilla ($p<0.001$) but not in the mandible. That was also reflected by the intercanine width change. Vertical canine movement seemed to be more predictable in the maxillary arch than in the mandibular arch, although the planned movement for the mandibular arch was greater.

Interpremolar expansion was accurate for both arches. Vertical movement of the mandibular first premolars did not show a significant discrepancy, but the median planned movement was only 0.2 mm.

For rotations, the findings were statistically significant for all teeth. The canines had the greatest discrepancies of 3.05° in the maxillary arch and 2.45° in the mandibular arch. The maxillary premolars had the lowest discrepancy of only 0.9°.

5.2 Clinical effectiveness of clear aligner treatment

5.2.1 Treatment outcome with orthodontic aligners and fixed appliances: A systematic review with meta-analyses (III)

The electronic literature search yielded 1376 results, while another seven were manually identified from the reference/citation lists of identified papers (Figure 16). After duplicate removal and screening the titles/abstracts of identified reports, the full texts of 343 papers were checked against the eligibility criteria. Ultimately, 11 papers pertaining to 11 unique studies (4 randomized and 7 retrospective non-randomized) were finally included, which were published as journal papers of dissertation/theses.

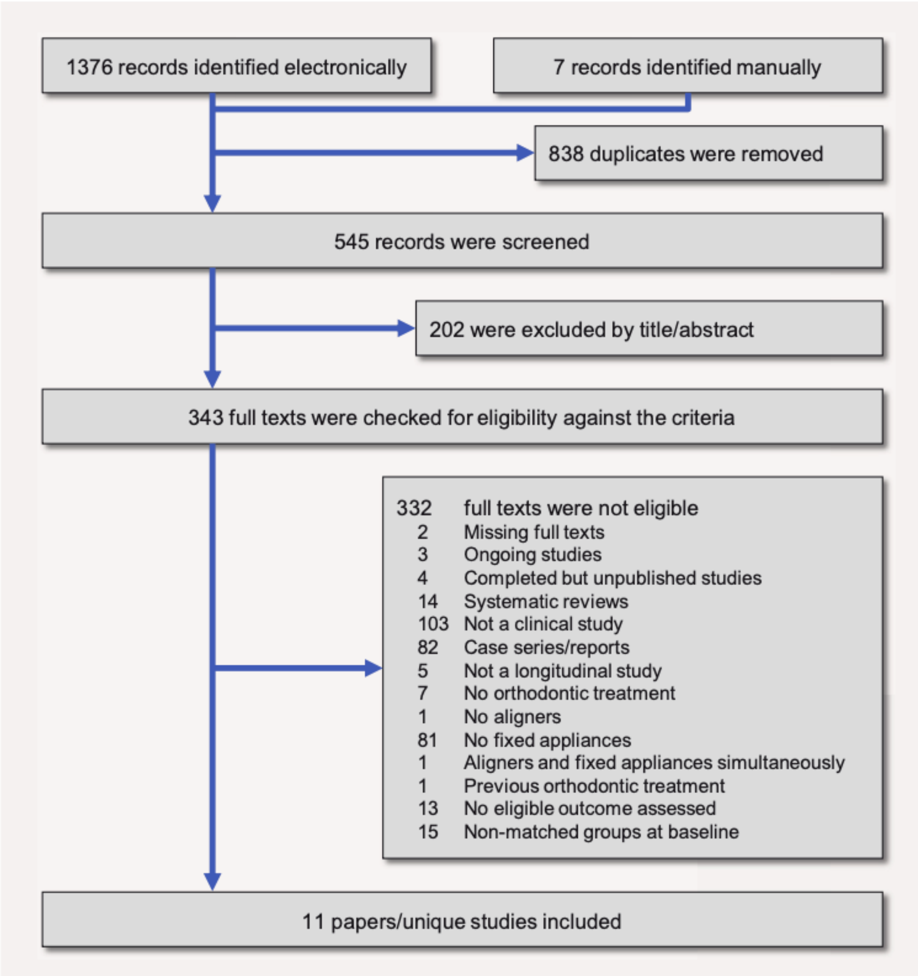

Figure 16. PRISMA flow diagram for the identification and selection of eligible studies in this review

The included studies were conducted in university clinics (n = 6; 55%), private practices (n = 4; 36%), or hospitals (n = 1; 9%) and originated from six different countries (Canada, China, Ireland, Italy, South Korea, and the United States of America) (Table 6). A total of 446 and 443 patients were treated with aligners and fixed appliances, respectively, with a median total sample of 66 patients per included study (range 19–200 patients per study). Out of the seven studies reporting on patient sex, 215 of the 661 patients in total were male (33%), while the mean patient age out of the nine studies reporting this was 28.0 years.

Table 6. Characteristics of included studies

Study	Design; setting; country*	Patients (M/F); age**	Malocclusion/ Tx	Appliance	Aligners/refinement/IPR(mm)	FU (mos)	Outcome
Abbate 2015 (47)	RCT; Uni; ITA	AL: 25 (NR); (10–18) FX: 22 (NR); (10–18)	NR/Non-Ex	AL: Invisalign® FX: Labial CLB	NR/NR/NR	BL, 3.0, 6.0, 9.0, 1 2.0 mos in Tx	PPD
Djeu 2005 (48)	rNRS; Pract; USA	AL: 48 (NR); 33.6 FX: 48 (NR); 23.7	DI: 19.3; Ex and Non-Ex .	AL: Invisalign® FX: Labial CLB (TE)	NR/NR/allowed	BL, END	ABO-OGS8; TxDur
Fetouh 2008 (49)	rNRS; Pract; USA	AL: 33 (NR); NR FX: 33 (NR); NR	Cl. I; mild crowding and overbite; DI: 3.22/Non-Ex	AL: Invisalign® FX: Labial CLB	NR/NR/NR	BL, END	ABO-OGS7
Gu 2017 (50)	rNRS; Pract; USA	AL: 48 (16/32); 26.0 FX: 48 (18/30); 22.1	PAR: 21.8; compliant/Non-Ex	AL: Invisalign® FX: Labial CLB (SW)	NR/38%/NR	BL, END	PAR; TxDur
Han 2015 (51)	rNRS; Uni; KOR	AL: 10 (2/8); 51.2FX: 9 (4/5); 47.3	Previous PerioDis; DI: 4.4/Non-Ex	AL: NR FX: Labial CLB	NR/NR/allowed	BL, END	ABL; PPD; TxDur
Hennessy 2016 (52)	RCT; Hosp; IRL	AL: 20 (6/14); 29.1 FX: 20 (7/13); 23.7	Mild crowding/Non-Ex	AL: Invisalign ® FX: Labial SLB (MBT)	18 ALs/allowed/ AL:FX 1.9:1.5	BL, END	IMPA; TxDur
Lanteri 2018 (53)	rNRS; Pract; ITA	AL: 100 (30/70); 28.0 FX: 100 (30/70); 25.0	PAR: 23.3/Non-Ex	AL: Invisalign® FX: Labial SLB (MBT)	43 ALs***/37%/ AL:FX 1.3:1.5	BL, END, 24.0 mos Post-Tx	PAR; RetFail; GingRec
Li 2015 (54)	RCT; Uni; CHN	AL: 76 (27/45); 35.2 FX: 76 (27/45); 32.2	DI: 27.4/Ex	AL: Invisalign® FX: Labial CLB	NR/NR/allowed (AL)	BL, END	ABO-OGS8; TxDur
Preston 2017 (55)	RCT; Uni; USA	AL: 22 (10/12); 27.8 FX: 22 (7/15); 25.4	Cl. I; mild crowding/ Non-Ex	AL: Invisalign® FX: Labial CLB (ALX)	NR/100% (2 refinements)/NR	BL, END, 1.0, 6.0 mos Post-Tx	ABO-OGS2; TxDur; contact areas
Robitaille 2016 (56)	rNRS; Uni; CAN	AL: 24 (11/13); 29.8 FX: 25 (6/19); 23.4	DI: 31.5/orthognathic surgery	AL: Invisalign® FX: Labial CLB	NR/NR/NR	BL, END	ABO-OGS8; TxDur
Yi 2018 (57)	rNRS; Uni; CHN	AL: 40 (9/31); 21.8 FX: 40 (11/29); 23.3	PAR: 22.6/Non-Ex	AL: NR FX: Labial CLB	NR/65%/NR	BL, END	PAR; TxDur; EARR

ABL: alveolar bone level, ABO-OGS: American Board of Orthodontists Objective Grading System (number of components assessed given in subscript), AL: aligner, ALX: Alexander technique, BL: baseline, Cl: (Angle's) Class, CLB: conventionally ligated brackets, DI: discrepancy index, EARR: external apical root resorption, END: end of comprehensive treatment, Ex: extraction, FU: follow-up, FX: fixed appliance, GingRec: gingival reces- sion, Hosp: hospital, IMPA: inclination of lower incisors to mandibular plane, IPR: interproximal enamel reduction, M/F: male/female, MBT: MacLaughlin–Bennet–Trevisi prescription, mo: month, NR: not reported, PAR: peer assessment rating, PerioDis: periodontal disease, PPD: periodontal probing depth, Pract: private

practice/clinic, RCT: randomized clinical trial, SLB: self-ligating bracket, SW: straightwire, TE: tip-edge, Tx: treatment, TxDur: treatment duration, Uni: university clinic.
*Countries given with their alpha-3 codes.
**Patient age is given either as mean (one value in without parenthesis) or if mean isn't reported as range (two values in parenthesis).
***Including refinement aligners.

As far as complexity of the treated cases is concerned, only six studies (55%) reported this with either the PAR index (n = 3; 27%) or the ABO DI (n = 3; 27%). Eight of the studies (73%) performed non-extraction treatment, one study (9%) both extraction and non- extraction treatment, and one study (9%) extraction treatment. The majority of studies (9/11 studies; 82%) reported on conventional comprehensive treatment, while one study (9%) reported on orthodontic treatment of patients with history of periodontal disease and one study (9%) reported on combined orthodontic/orthognathic treatment. Details of the aligner treatment were only partly reported among the included studies with only two studies (18%) reporting the number of aligners, four studies (36%) reporting on 'refinement' rate (i.e., the mid-course re-evaluation and planning of additional aligners), and two studies (18%) on the actual amount of interproximal enamel reduction performed during treatment in both groups. The included studies reported on a wide spectrum of treatment outcomes, with only three studies reporting on the complete ABO-OGS score including all eight components, as well as failure of the case to pass the ABO criteria for adequate occlusal results (ABO-OGS score < 30 points). One study reported on the ABO-OGS score of seven out of eight components (excluding root angulation) and also excluded scoring the second molars without any justification. One study also reported solely on two of the eight ABO-OGS components, namely marginal ridges and buccolingual inclination. Three studies used the PAR index and reported either post-treatment PAR scores or PAR reductions. Eight studies reported on treatment duration, though considerable variation in the reported results was seen. Finally, single studies reported on periodontal probing depth, alveolar bone loss, EARR, lower incisor inclination, and gingival recessions.

The included randomized trials presented several issues that increased their risk for bias. Two trials were in high risk of bias due to problems in the randomization process, deviations from intended interventions, missing outcome data, and outcome measurement. The remaining two trials were in low risk of bias, except from the fact that no a priori trial protocol could be found to rule out selective reporting. The included non-randomized studies were in considerably higher risk of bias, with five of them presenting moderate risk of bias, one of them serious risk of bias, and one of them critical risk of bias. Their main shortcomings pertained to confounding, selection of participants into the study, deviations from intended interventions, outcome measurement, and selection of the reported result.

For all included studies the data reported in the paper were used, while for one study without matching[165] the author provided raw data that were used to extract a matched sub-sample to include. The results of all individual trials and the results of the meta-analyses of at least two studies are found in Table 7.

Table 7. Results of random-effects meta-analyses for eligible outcomes with at least two contributing studies comparing aligners to fixed appliances. *

Outcome*	n	Effect	P	I^2 (95% CI)	tau^2 (95% CI)	95% prediction
ABO-OGS total score	2	MD: 13.38 (9.45, 17,31)	<0.001**	0% (0%, 98%)	0 (0, 371.98)	NC
ABO-OGS failure (score>30)	2	RR: 1.63 (1.24, 2.13)	<0.001**	0% (0%, 99%)	0 (0, 4.47)	NC
ABO-OGS component 1: alignment	2	MD: 2.60 (-0.48, 5.69)	0.10	89% (24%, 100%)	4.40 (0.18, 622.82)	NC
ABO-OGS component 2: marginal ridges	2	MD: 0.60 (-0.22, 1.43)	0.15	0% (0%, 98%)	0 (0, 21.95)	NC
ABO-OGS component 3: buccolingual inclination	2	MD: 1.14 (0.21, 2.07)	0.02+	0% (0%, 99%)	0 (0, 59.04)	NC
ABO-OGS component 4: occlusal contacts	2	MD: 4.45 (2.72, 6.18)	<0.001**	0% (0%, 98%)	0 (0, 85.36)	NC
ABO-OGS component 5: occlusal relationship	2	MD: 1.39 (-0.12, 2.89)	0.07	28% (0%, 99%)	0.33 (0, 148.14)	NC
ABO-OGS component 6: overjet	2	MD: 2.61 (1.29, 3.93)	<0.001**	0% (0%, 98%)	0 (0, 61.18)	NC
ABO-OGS component 7: interproximal contacts	2	MD: 0.02 (-0.17, 0.21)	0.83	0% (0%, 98%)	0 (0, 2.71)	NC
ABO-OGS component 8: root angulation	2	MD: 0.87 (0.46, 1.28)	<0.001**	0% (0%, 98%)	0 (0, 6.63)	NC
PAR post-Tx	2	MD: -0.03 (-2.02, 1.96)	0.98	83% (0%, 100%)	1.72 (0, 258.55)	NC
PAR reduction via Tx	3	MD: -1.76 (-3.62, 0.10)	0.06	41% (0%, 96%)	1.13 (0, 42.78)	-19.88, 16.36
PAR great improvement (reduction>30)	2	RR: 0.72 (0.40, 1.28)	0.26	66% (0%, 100%)	0.12. (0, 22.56)	NC
Treatment duration (months)	7	MD: -0.55 (-3.73, 2.63)	0.73	94% (82%, 99%)	16.25 (4.74, 73.67)	-11.72, 10.62

ABO-OGS, American Board of Orthodontists Objective Grading System; CI, Confidence Interval; MD, Mean Difference; n, number of contributing studies; NC, Non-Calculable; PAR, Peer Assessment Rating; RR, Relative Risk.
** statistically significant findings at the 5% level.
*with bold are given meta-analyses being both statistically significant and clinically relevant – judged as having an effect being at least equal to the average standard deviation of the control (fixed appliance) group across included studies or a relative risk of at least 2.

Fourteen different meta-analyses could be conducted pertaining to the review's primary outcome (ABO-OGS scores), PAR scores, and treatment duration. A meta-analysis of two studies indicated that treatment with aligners was associated with significantly worse ABO-OGS scores compared to braces (MD = 13.4 points greater; 95% CI = 9.5–17.3 points greater; p=0.002), which was also clinically relevant (Table 8, Figure 17).

Table 8. Summary of findings table according to the GRADE approach.

Outcome [follow-up] Studies (patients)	Relative effect (95% CI)	Fixed appliance[a]	Aligners	Difference in Aligner group	Quality of the evidence (GRADE)[b]	What happens with aligners
ABO-OGS score [post Tx] 145 patients (2 studies)	-	29.9 pts	-	13.4 pts greater (9.5 to 17.3 greater)	+++ Moderate[c,d] due to bias	Probably leads to worse finishing quality (higher ABO-OGS scores)
Unacceptable finishing quality (ABO-OGS score>30 pts) [post Tx] 145 patients (2 studies)	RR 1.6 (1.23 TO 2.13)	48.0%	78.2% (59.0%-100.0%)	30.2% more (11.0% to 52.0% more)	+++ moderate[c] due to bias	Probably leads to more patients with unacceptable finishing quality
PAR reduction [post Tx] 376 patients (3 studies)	-	19.5 pts	-	1.8 pts less (3.6 less to 0.1 more)	++ low[c] due to bias	Little to no difference in treatment efficacy (smaller reduction in PAR scores)
Great improvement in PAR (PAR reduction>30 pts) [post Tx] 296 patients (2 studies)	RR 0.7 (0.40 to 1.28)	46.0%	33.0% (18.5%-58.5%)	13.0% less (27.5% Less to 12.8% more)	++ low[c] due to bias	Little to no difference in patients with great improvement in PAR scores
Treatment duration [post Tx] 607 patients (7 studies)	-	19.6 mos	-	0.6 mo shorter (3.7 shorter to 2.6 longer)	+ very low[f,g] due to bias, inconsistency	Too heterogenous response to synthesize across studies
EARR as % of anterios' root Length [post Tx] 80 patients / 640 teeth (1 study)	-	7.0%	-	1.8% less (1.3% to 2.4% less)	++ low[e] due to bias	Might lead to greater EARR
Inclination of lower incisors [near Tx end] 44 patients (1 study)	-	5.3°	-	1.9° less (4.1° less to 0.3° more)	++ low[h,i] due to bias, imprecision	Little to no difference in lower incisor inclination
Gingival recession [2 years post Tx] 158 patients (1 study)	RR 0.9 (0.31 to 2.68)	8.0%	7.2% (2.5%-21.4%)	0.8% less (5.5% Less to 13.4% more)	+++ moderate[c] due to bias	Little to no difference in gingival recession

Intervention: comprehensive orthodontic treatment with thermoplastic aligners versus fixed appliances / Population: adolescent or adult patients with any kind of malocclusion / Setting: university clinics, private practice, hospital (Canada, China, Ireland, Italy, USA).

a Response in the control group is based on average response of included studies (random-effects meta-analysis).

b Starts from "high"

c Downgraded by one level for bias due to the inclusion of non-randomized studies with moderate risk of bias

d Potentially great effect observed (larger than one average standard deviation), but no upgrading due to residual confounding.

e Downgraded by two levels for bias due to the inclusion of non-randomized studies with critical / serious risk of bias.

f Downgraded by two levels for bias due to the inclusion of randomized trials with high risk of bias and non-randomized studies with serious/critical risk of bias.

g Downgraded by one level due to inconsistency; great variability is seen among included studies with significant studies arranged on both sides of the forest plot (confident signs of heterogeneity that influence our decision about which treatment is shorter, which precludes calculating an average effect)

h Downgraded by one level for bias due to the inclusion of a randomized trial with high risk of bias.

i Downgraded by one levels for imprecision due to the inclusion of an inadequate sample.

ABO-OGS, American Board of Orthodontists Objective Grading System; CI, confidence interval; EARR, external apical root resorption; GRADE, Grading of Recommendations Assessment, Development and Evaluation; PAR, peer assessment rating; pt, point; Tx, treatment.

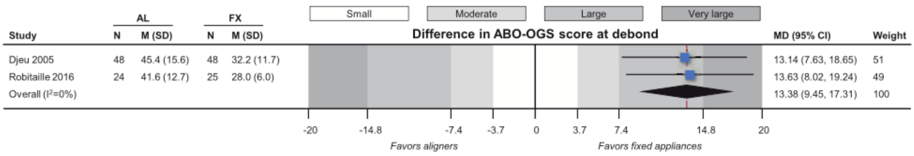

Figure 17. Contour-enhanced forest plot on the comparison of total ABO-OGS scores post-treatment between aligners and fixed appliances. ABO-OGS, American Board of Orthodontists Objective Grading System; AL, aligner; CI, confidence interval; FX, fixed appliance; M, mean; MD, mean difference; N, number of patients; SD, standard deviation. Contours correspond to different effect magnitude and the red dotted line corresponds to 95% random-effects prediction.

Additionally, patients treated with aligners were significantly more likely to be finished to an unacceptable quality according to the ABO standards and fail the ABO examination criteria (ABO-OGS score > 30) compared to those treated with braces (3 studies; RR = 1.6; 95% CI = 1.2–2.0; p< 0.001; Table 8). No considerable heterogeneity across studies was seen, which reported a small to moderate increase in the rate of suboptimal finishing quality. On absolute terms these corresponded to ABO 'fail rates' of 60.6% and 38.9% for aligners and braces, respectively. This is translated to an NNT of 5, which means that every fifth case treated with aligners instead of fixed appliances would fail the ABO examination, but would get a 'passing' grade if it was treated with fixed appliances, which is a potentially clinically relevant effect.

Looking at the comparative performance for each separate component of ABO-OGS between aligners and braces gives a more precise image about the occlusal aspects mostly affected by the treatment modality (Table 8; Figure 18). Overall, meta-analyses of three studies indicated that five of the eight aspects of the occlusion were finished significantly worse with aligners than with fixed appliances: buccolingual inclination (MD: 0.8 point; 95% CI: 0.5-1.1 point; p<0.001), occlusal contacts (MD: 3.1 points; 95% CI: 0.6-5.6 points; p=0.02), occlusal relationship (MD: 1.0 point; 95% CI: 0.6-1.4 points; p<0.001), overjet (MD: 1.8 points; 95% CI: 0.6-3.0 points; p=0.002), and root angulation (MD: 0.8 point; 95% CI: 0.5-1.1 point; p<0.001). Looking carefully at the effect magnitude it is obvious that the clinical relevance for each separate criterion is questionable, as small to moderate differences between aligners and braces are seen on average. However, when adding all these differences for each criterion, a clinically relevant worse treatment outcome is seen with aligners overall.

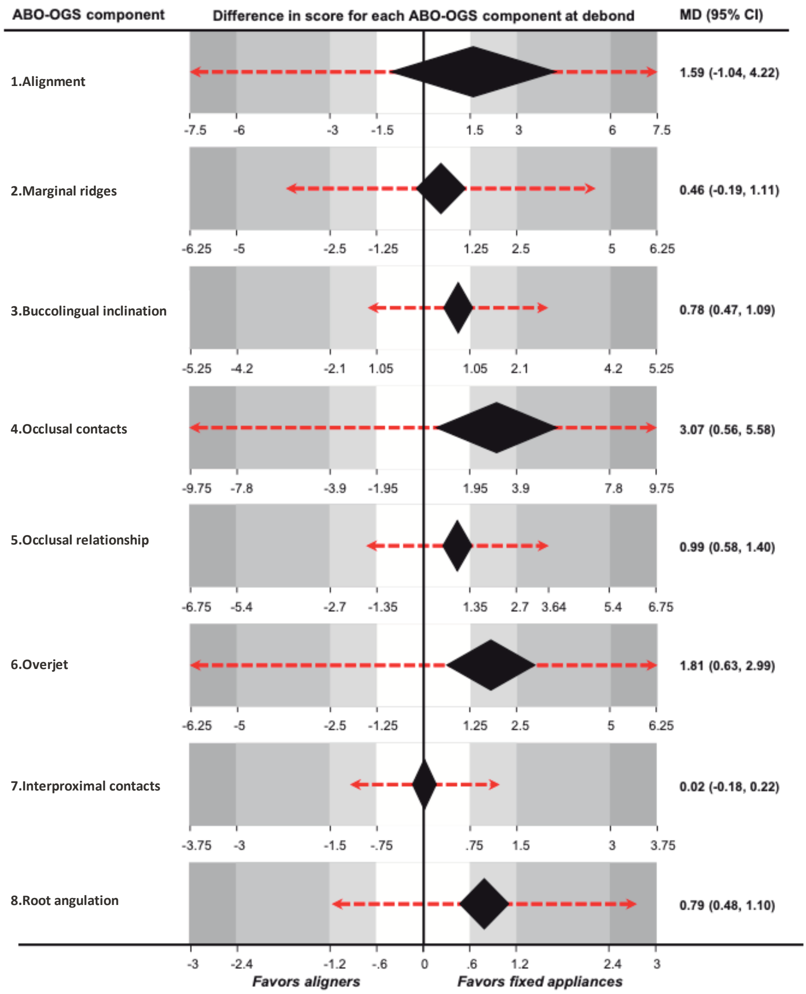

Figure 18. Composite contour-enhanced forest plot illustrating the summary results of 8 meta-analyses (each with 3 studies and 297 patients) for the comparison of each separate ABO-OGS component between orthodontic aligners and fixed appliances. ABO-OGS, American Board of Orthodontists Objective Grading System; CI, confidence interval; MD, mean difference. Contours correspond to different effect magnitude and the red dotted lines correspond to 95% random- effects predictions.

Looking at the occlusal outcome of treatment through meta-analyses using the PAR index gives a slightly different picture (Table 8). Overall, no statistically significant difference between aligners and braces was detected either by post-treatment absolute values (2 studies; p=0.98) or by PAR reduction (3 studies; p=0.06). Likewise, no difference in the proportion of patients experiencing a great improvement in their PAR scores through treatment (PAR reduction of at least 22 points or PAR score of 0 post-treatment) was seen (2 studies; p=0.26).

Considerable variation was seen in the effect of treatment modality on treatment duration. Meta-analysis of seven studies indicated that on average no definite conclusions can be drawn regarding treatment duration with either aligners or fixed appliances (MD: -0.6 month; 95% CI: -3.7 to 2.6 months; p= 0.73). Extreme heterogeneity was seen across studies (I^2 = 94%), which makes the ability to synthesize existing studies into a single estimate questionable (Figure 19). Specifically, two studies reported statistically significant reduction in treatment duration with aligners, two studies reported statistically significant increase in treatment duration with aligners, while the remaining three studies did not find statistically significant differences. Furthermore, exclusion of a study assessing combined orthodontic/orthognathic treatment[166] instead of only orthodontic treatment did not improve the results (6 studies; MD: -0.1 month; 95% CI: -3.5 to 3.4 months; I^2 = 95%). Nor was the situation improved by limiting the meta-analysis to only randomized trials (2 studies; MD: 2.69 months; 95% CI: -5.0 to 10.4 months; I^2 = 96%) or to only studies with non-extraction treatment (5 studies; MD: 0.6 month; 95% CI: -3.2 to 4.4 months; I^2 = 96%). Therefore, it is logical to assume that treatment duration is influenced by additional confounding variables and that the choice of appliance alone does not have a consistent influence on treatment duration.

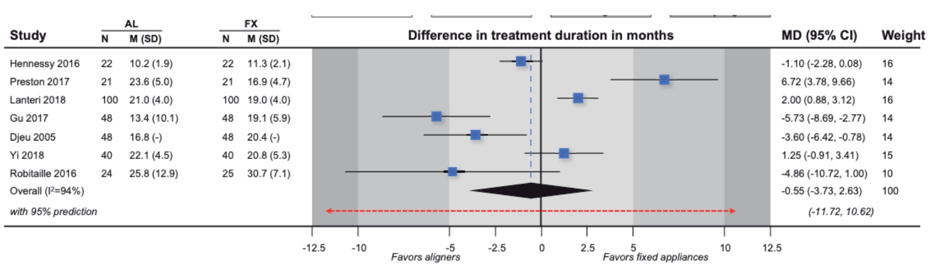

Figure 19. Contour-enhanced forest plot on the comparison of treatment duration in months between aligners and fixed appliances. AL, aligner; CI, confidence interval; FX, fixed appliance; M, mean; MD, mean difference; N, number of patients; SD, standard

deviation. Contours correspond to different effect magnitude and the red dotted line corresponds to 95% random-effects prediction.

Additionally, several outcomes were assessed by single studies that provide only limited insights. Results of a single study[167] indicated that aligners were worse in terms of reduction for the PAR component for upper anteriors (MD: -1.0 point; 95% CI: -1.9 to -0.1 point; p=0.02) and overbite (MD: -1.0 point; 95% CI: -1.9 to -0.2 points; p=0.02) compared to braces. The results of a single study[167] indicated that aligners were more efficient in terms of PAR reduction/month of treatment compared to fixed appliances (MD: 0.4 point/month; 95% CI: 0.1-0.7 point/ month; p=0.01). However, as the same study reported that aligners were overall associated with smaller reductions in the PAR scores than fixed appliances, looking at the PAR reduction/month might be misleading.

As far as adverse effects of treatment are concerned, a single identified study on EARR[168] reported that significantly smaller percentage of the incisors' root was resorbed during treatment compared to fixed appliances (MD: -1.8%; 95% CI: -2.4% to -1.3%; p<0.001). The same was seen for the various subgroups according to tooth type (central versus lateral incisor) and jaw (maxilla versus mandible), but the effect magnitude was on average very small and probably of no clinical relevance. Additionally, treatment with aligners was not associated in a single included study[169] with significantly lower proclination of the lower incisors compared to fixed appliances (p=0.10). However, it must be noted that a very small sample was included, which makes the study probably under-powered to identify such a small difference of 1.9° between groups, if it really exists. Furthermore, no significant difference in the development of gingival recessions 2 years after treatment with aligners or fixed appliances was seen in another single study (MD: 0.9; 95% CI: 0.3-2.7; p=0.86)[170].

Finally, limited evidence on the effect of appliance choice on loss of periodontal attachment was provided by a single identified study[165], which assessed orthodontic alignment of anterior teeth in adult patients with previous history of treated periodontal disease and found no differences between aligners and braces for periodontal probing depth (p=1.00) or alveolar bone levels (p= 0.69). On the other side, fixed appliances were significantly quicker repositioning the patients' migrated anterior teeth compared to aligners (3.9 versus 6.0 months; MD: -2.1 months; 95% CI: -3.7 to -0.5 months; p=0.01).

Several subgroup analyses, meta-regressions, and assessments for reporting biases were originally planned in the review's protocol, but could ultimately not be performed due to limited data and inadequate reporting.

The quality of evidence for the seven meta-analyses ranged from high to very low, as methodological limitations introducing bias, inconsistency, and imprecision were identified on some cases (Table 8). The two meta-analyses with significant differences in the ABO-OGS scores were supported by evidence of moderate quality, which indicates that these results are likely to be close to the estimate of the true effect. A GRADE rating of low was assigned to the significant difference in EARR, which however might be markedly different from the estimate of the true effect. Finally, the remaining five non-significant meta- analyses were supported by evidence of moderate to very low quality. The main reason for downgrading the quality of evidence pertained to the inclusion of non-randomized studies with serious/critical methodological issues that most probably introduce bias. This was especially seen in the retrospective study of Gu et al.[167] that selectively reported data from what might be regarded as 'good' cases, while excluding patients with issues of compliance or oral hygiene. This means that further research in terms of well-designed studies is very likely to have an important impact, which is likely to change our current estimates of effect.

The sensitivity analyses by omitting non-randomized studies indicated relative robustness of the results (Table 9), apart from the observed reduced statistical power of the sensitivity analyses, which was expected after omitting trials.

Table 9. Sensitivity analysis by omitting non-randomized studies.

	Original analysis			Sensitivity analysis		
Outcome	n	Effect (95% CI)	P	n	Effect (95% CI)	P
Treatment duration (months)	7	MD: -0.55 (-3.73, 2.63)	0.73	2	MD: 2.69 (-4.97, 10.35)	0.49
ABO-OGS total score	2	MD: 13.38 (9.45, 17.31)	<0.001*	0	-	
ABO-OGS failure (score>30)	2	RR: 1.63 (1.24, 2.13)	<0.001*	0	-	
ABO-OGS component: alignment	2	MD: 2.60 (-0.48, 5.69)	0.10	0	-	
ABO-OGS component: marginal ridges	2	MD: 0.60 (-0.22, 1.43)	0.15	0	-	
ABO-OGS component: buccolingual	2	MD: 1.14 (0.21, 2.07)	0.02*	0	-	
inclination	2	MD: 4.45 (2.72, 6.18)	<0.001*	0	-	
ABO-OGS component: occlusal contacts	2	MD: 1.39 (-0.12, 2.89)	0.07	0	-	
ABO-OGS component: occlusal relationship	2	MD: 2.61 (1.29, 3.93)	<0.001*	0	-	
ABO-OGS component: overjet	2	MD: 0.02 (-0.17, 0.21)	0.83	0	-	
ABO-OGS component: interproximal contacts	2	MD: 0.87 (0.46, 1.28)	<0.001*	0	-	
ABO-OGS component: root angulation	2	MD: -0.03 (-2.02, 1.96)	0.98	0	-	
PAR post-Tx	3	MD: -1.76 (-3.62, 0.10)	0.06	0	-	
PAR reduction via Tx						

ABO-OGS, objective grading system of the American Board of Orthodontics; CI, confidence interval; MD, mean difference; PAR, peer assessment rating; RR, relative risk; Tx, treatment.

5.3. Effects of cleansers and attachments on the surface topography and structure of clear aligners

5.3.1 Effect of cleansers on the composition and mechanical properties of orthodontic aligners in vitro (IV)

The RB and RC cleansers showed a similar pH value (6.31±0.02), whereas the ST cleanser showed a significantly lower pH value (4.83 ± 0.04). Figure 20 demonstrates representative force–indentation depth (a, c) and force–time curves (b, d) for the aligners (C, I) per cleaner group (RB, RC, ST) and the control (CO).

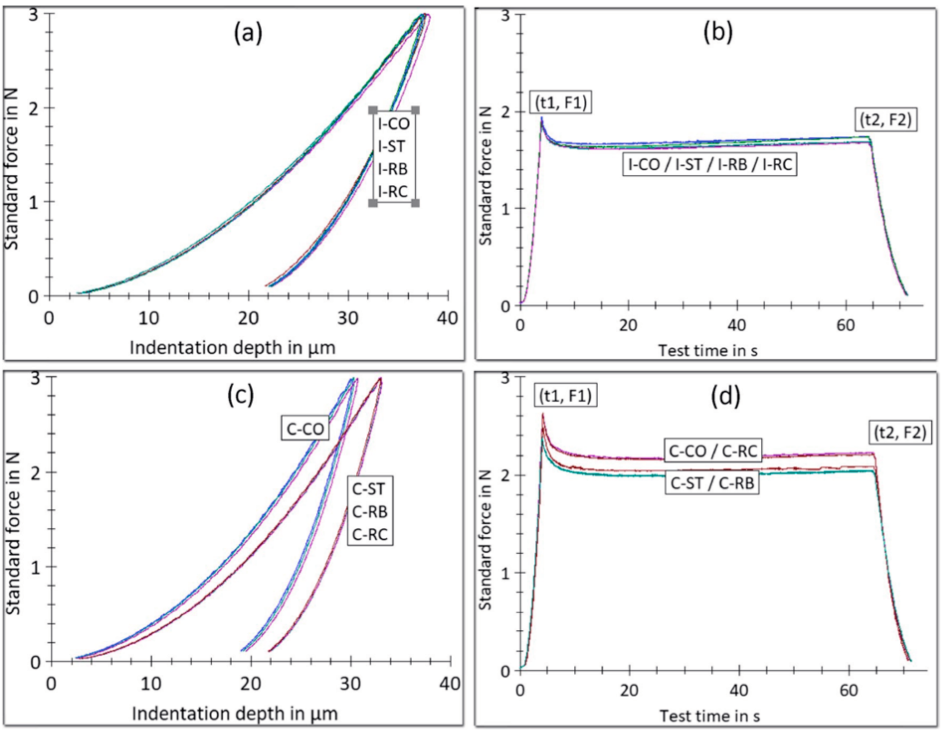

Figure 20. Representative force–indentation depth (a, c) and force–time curves (b, d) for Clear Aligner (C) and Invisalign (I) appliances after immersion in Retainer Brite (RB), Retainer Cleaner (RC) and Steraligner (ST) solutions vs the controls (CO).

For Clear Aligner, a shifting of the peak of the load– indentation graph was found toward higher indentation values after all cleaner treatments in comparison with the control (a), which implies a softening effect. Moreover, two of the cleaner treatments (RB, ST) demonstrated lower force decay overtime from RC and the control (b). The results are summarized in Table 10. All the cleaners comprised a statistically homogeneous group with significantly lower HM, n_{IT} values from the control. Insignificant differences were found between the groups in E_{IT}, whereas the R_{IT} measurements revealed significantly reduced values of RB, ST groups from RC and the control (CO).

Table 10. The results of the IIT-derived mechanical properties for Clear Aligner (C)

Group	HM (N/mm^2)	E_{IT} (MPa)	n_{IT} (%)	R_{IT} (%)
C-CO	112 (6)^a	2699 [2413 2991]	40.6(0.7)^a	8.4 [7.9 12.8]^a
C-RB	106 (3)^b	2469 [2409 3034]	39.0 (0.6)^b	15.1 [14.1 15.6]^b
C-RC	108 (1)^b	2529 [2352 3041]	39.1 (0.5)^b	9.0 [8.4 9.2]^a
C-ST	107 (3)^b	2466 [2376 2643]	38.6 (0.6)^b	12.1 [8.7 13.3]^b

Mean values and standard deviations (in parentheses) or median and 25% and 75% percentiles (in brackets).
Same superscript letters show groups without statistical differences per property ($p > 0.05$)

For Invisalign, the loading and unloading curves were identical (a, b) indicating insignificant differences between the cleaner groups tested and the control, as is verified from the numerical data given in Table 11.

Table 11. The results of the IIT-derived mechanical properties for Invisalign (I)

Group	HM (N/mm^2)	E_{IT} (MPa)	n_{IT} (%)	R_{IT} (%)
I-CO	80 (4)	1615 (148)	44.7 [44.2 45.9]	9.3 [6.5 11.4]
I-RB	80 (5)	1605 (141)	43.6 [42.4 44.6]	9.2 [6.9 12.3]
I-RC	79 (4)	1558 (197)	46.0 [45.0 46.6]	8.5 [7.6 9.2]
I-ST	83 (5)	1709 (148)	45.6 [45.2 46.4]	9.6 [5.4 13.8]

Mean values and standard deviations (in parentheses) or median and 25 and 75% percentiles (in brackets). No statistically significant differences were found between the immersion groups and the control for the properties tested ($p > 0.05$)

Representative ATR-FTIR spectra of the aligners before and after cleaning treatments are illustrated in Figures. 21, 22 and 23.

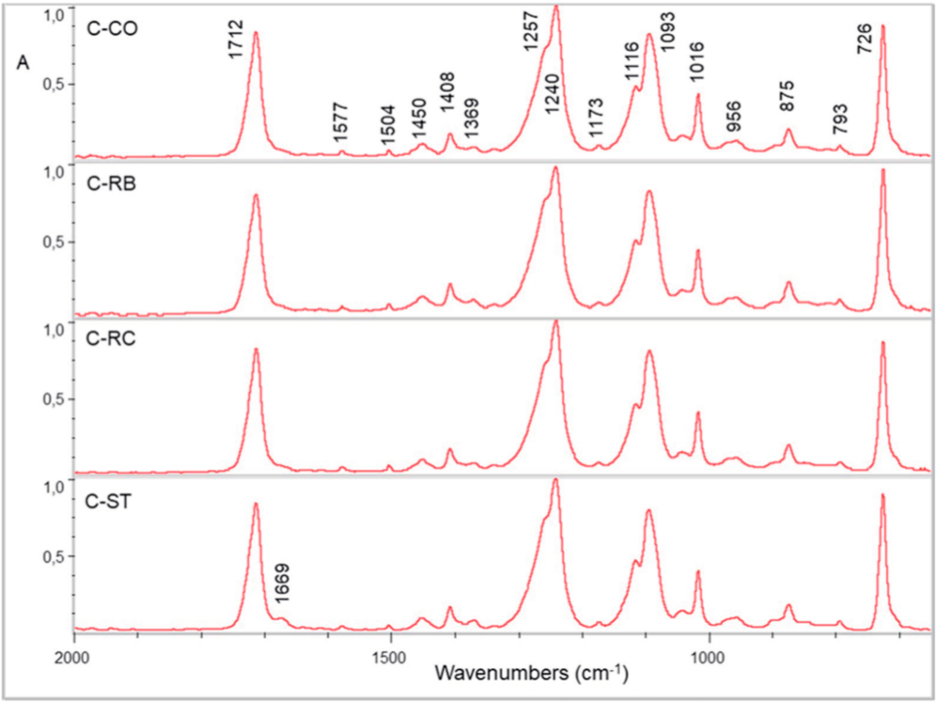

Figure 21. ATR-FTIR spectra of Clear Aligner (C) before (CO) and after treatments with Retainer Brite (RB), Retainer Cleaner (RC) and Steraligner (ST) cleaners. An additional peak appeared at 1669 cm^{-1} after ST cleaner (expanded 2000–650 cm^{-1} range, absorbance scale)

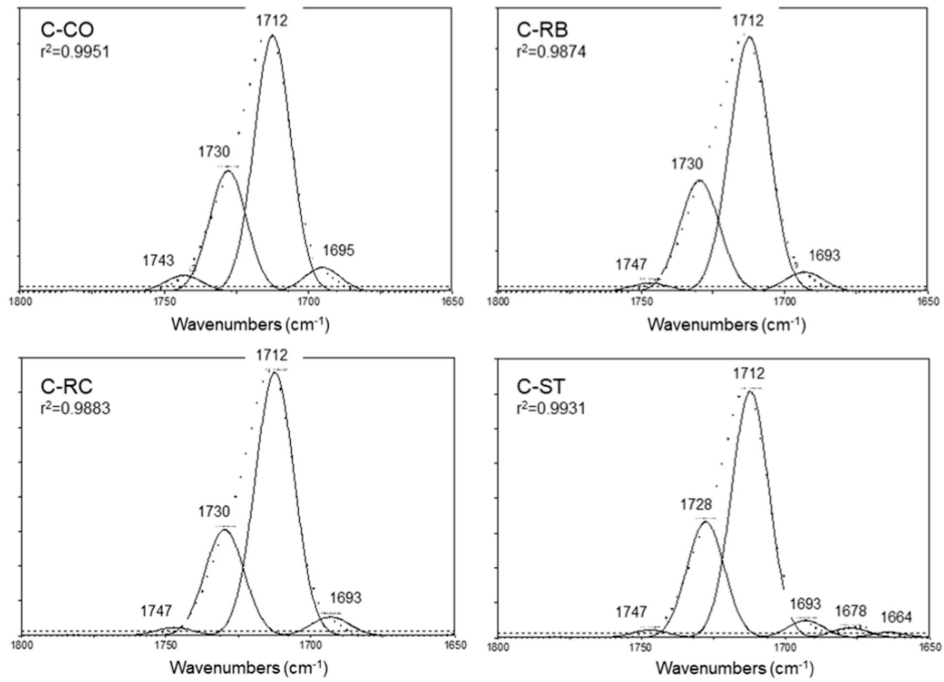

Figure 22. Gaussian curve-fitting of the ester peak of Clear Aligner before (CO) and after treatments with Retainer Brite (RB), Retainer Cleaner (RC) and Steraligner (ST) cleaners. The additional peak after ST cleaner at 1669 cm^{-1} of Fig. 19 is analyzed in two peaks at 1678 cm^{-1} and 1664 indicating formation of acid derivatives (1800–1650 cm^{-1} range, absorbance scale, dotted lines: original spectra, r^2: coefficient of determination for the goodness of curve-fit)

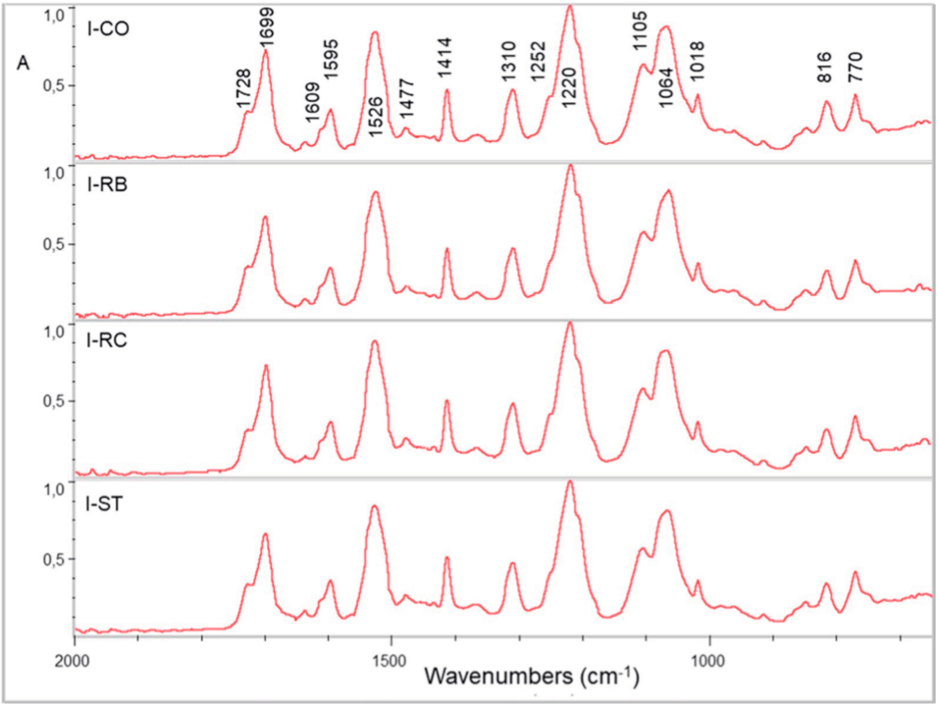

Figure 23. ATR-FTIR spectra of Invisalign (I) before (CO) and after treatments with Retainer Brite (RB), Retainer Cleaner (RC) and Steraligner (ST) cleaners. Spectra are identical (expanded 2000–650 cm^{-1} range, absorbance scale)

For Clear Aligner (Figure. 21), the peak assignments are as follows (cm^{-1}): 2926 and 2854 (C–H stretching) [not shown in the expanded spectra of the figure]; 1712 (C=O stretching); 1577, 1604 (aromatic C–C stretching); 1450, 1408, 1369 (C–H bending); 1257, 1240 (C=O stretching), 1173 (C–H bending); 1113, 1093 (C–O– stretching); 1016 (C–C ring bending), 956 (C–H stretching of the cyclohexylene ring); 875, 723 (aromatic C–H bending)[40,171,172]. The cleaning procedures showed similar spectra, except for ST, which demonstrated a small peak at 1670 cm^{-1} assigned to acid groups[173]. The curve- fit analysis of the ester peak of Clear Aligner (Figure 22 and Table 12) showed two major peaks at 1727 cm^{-1} (free C=O groups) and 1712 cm^{-1} (H–bonded C=O groups) comprising 90–93% of the total C=O peak area ($tA_{C=O}$) at a ratio of 0.4–0.5 (free to H–bonded, based on mean values) for RB, RC and CO, ST, respectively. All specimens showed minor peaks at 1740 cm^{-1} (2–4% of $tA_{C=O}$) and 1693 cm^{-1} (5–6% of $tA_{C=O}$) possibly assigned to oxidation by-products.

Table 12. The results of the curve-fitting analysis of the ester peak for Clear Aligner (C)

Group	Peak area (%)					
	1743 cm^{-1}	1727 cm^{-1}	1712 cm^{-1}	1693 cm^{-1}	1677 cm^{-1}	1664 cm^{-1}
C-CO	3.9	29.1	61.3	5.7	-	-
C-RB	2.1	28.5	64.6	4.8	-	-
C-RC	2.1	26.9	66.2	4.8	-	-
C-ST	1.9	27.7	60.4	4.1	3.4	2.5

1727 cm^{-1}: Free C=O groups; 1712 cm^{-1}: H–bonded C=O groups; 1743, 1693 cm^{-1}: Oxidation byproducts; 1677, 1664 cm^{-1}: Acid impurities

The control group demonstrated approximately twice the area of the 1740 cm^{-1} peak in comparison with the treated groups (4 vs 2 for ST and 2.1 for RB, RC), whereas the differences in the 1690 cm^{-1} peak area were smaller (5.7 vs 4.1 for ST and 4.8 for RB, RC). The ST group demonstrated additionally two low wavenumber peaks (1677 and 1644 cm^{-1}, 5.9% in sum of $tA_{C=O}$) attributed to acid formation[173].

For Invisalign (Figure 23), the peak assignments are as follows (cm^{-1}): 3330–3270 (N–H stretching); 2927–2919 and 2850 (C–H stretching) [not shown in the expanded spectra of the figure]; 1726–1699 (C=O stretching); 1609 and 1595 (aromatic C–C stretching); 1526 (C–N and N–H bending); 1477, 1412, 1365 (C–H bending); 1310 (C=O vibrations), 1252 (C–N and C–O stretching); 1220, 1105, 1064 and 1017 (C–O–C stretching) 816 and 770 (aromatic C–H bending)[40,174]. No differences were found after the cleaning treatments and the controls.

The curve-fit analysis of the ester peak of Invisalign (Figure 24 and Table 13) resolved four peak components assigned to polyurethane (hard polymer segment) or polycarbonate (soft polymer segment) of poly(ester-urethane) polymers at 1732 cm^{-1} (free C=O groups of urethane and carbonate components), 1714 cm^{-1} (H–bonded C=O groups of carbonate component), 1699 cm^{-1} (H–bonded C=O groups of amorphous urethane component) and 1683 cm^{-1} (H–bonded C=O groups of low-ordered urethane component)[175]. The free C=O accounted for 16.7–18.2% of the $tA_{C=O}$ (mean values) and were not affected by the treatments. The same applied for the H–bonded C=O groups of the carbonate segment (21.7–23.8%). However, for the amorphous urethane H–bonded C=O groups, a reduction in the peak area was found after RB treatment (39.8%) in comparison with the control (50.5%) and the other treatments (50.3% for RC and 44.3% for ST). This difference was in favour of the low-ordered urethane H-bonded C=O groups, which increased after RB treatment (16.3%) in comparison with the control (9.8%), RC (11%) and ST (8.6%).

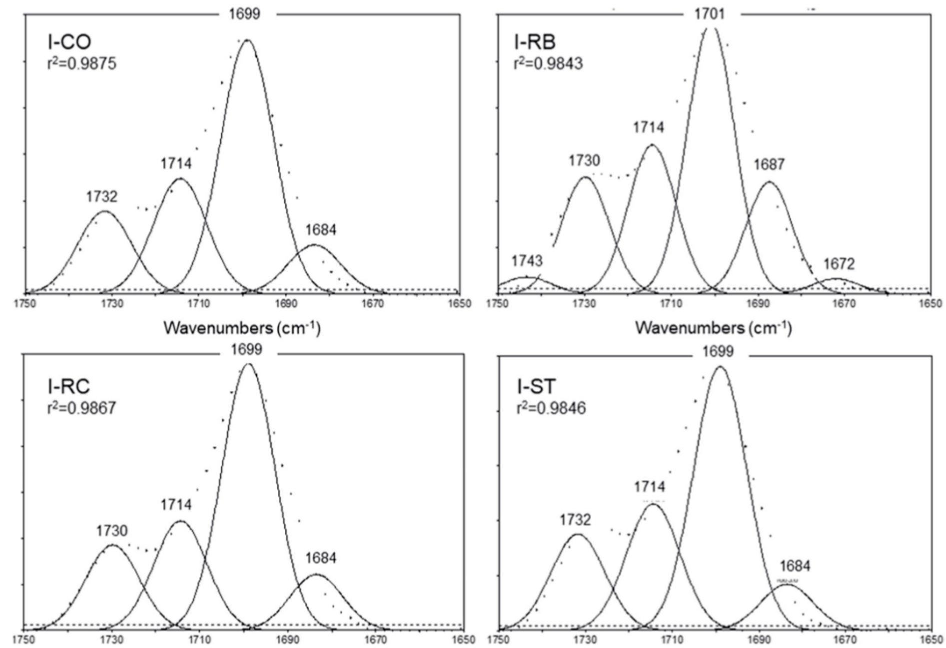

Figure 24. Gaussian curve-fitting of the ester peak of Invisalign (I) before (CO) and after treatments with Retainer Brite (RB), Retainer Cleaner (RC) and Steraligner (ST) cleaners. After RB treatment, two additional peaks appeared (1743 cm^{-1}, 1672 cm^{-1}) and the intensity of the peak at 1687 $cm^{-1}$was increased indicating changes in the H–bonding status of the ester groups (1750–1650 cm^{-1} range, absorbance scale, dotted lines: original spectra, r^2: coefficient of determination for the goodness of curve-fit)

Table 13. The results of the curve-fitting analysis of the ester peak for Invisalign (I)

Group	**Peak area (%)**					
	1743 cm^{-1}	**1732 cm^{-1}**	**1714 cm^{-1}**	**1699 cm^{-1}**	**1684 cm^{-1}**	**1672 cm^{-1}**
C-CO	-	16.7	23	50.5	9.8	-
C-RB	2.5	17.2	21.9	39.8	16.3	2.3
C-RC	-	17	21.7	50.3	11	-
C-ST	-	18.2	23.8	44.3	8.6	-

1732 cm^{-1}: Free C=O groups of urethane and carbonate; 1714 cm^{-1}: H–bonded C=O groups of urethane and carbonate; 1699 cm^{-1}: H–bonded C=O groups of amorphous urethane segments; 1684 cm^{-1}: H–bonded groups of low-ordered urethane segments; 1743, 1672 cm^{-1}: Acid impurities

5.3.2 Surface alterations of resin composite attachments induced by orthodontic aligners: An in-vitro study (unpublished data)

Representative stereomicroscopic images of the zirconia frames with the composite attachments after removal and re-seating of the aligners are illustrated in Figure 25. The debonding rate in Group I (sculptable composite) was estimated as to 14.1% whereas in Group 2 (flowable composite) as to 31.3%. Low magnification morphological features of Group I and II attachments bonded on various teeth for the two conditions (removed/reseated and control) are presented in Figures 26 and 27. The characteristic abrasion-induced defects by removal and re-seating of the aligners were scratches on the labial/buccal attachment free-surfaces, marginal defects mainly at the cervical regions with fracture or rounding of the attachment edges and angles, and in some cases loss of the characteristic surface texturing, which is mainly attributed to the topography of the aligner surfaces facing the teeth, due to the manufacturing process. The flowable composite (Group II) demonstrated higher frequency of texturing loss and bulk attachment fractures. The control groups (no removal/reseating of the aligners) demonstrated a textured surface morphology, with no marginal defects (Figure 28).

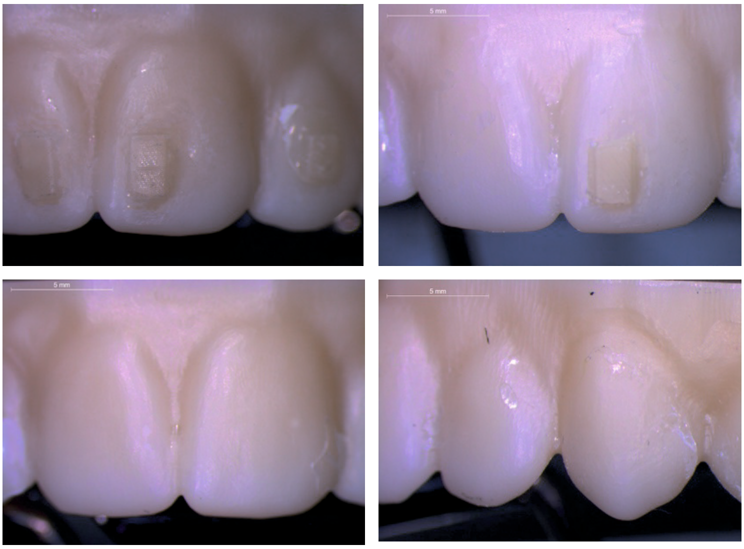

Figure 25. Stereomicroscopic images of zirconia frames with sculptable (Group I, upper row) and flowable (Group II, lower row) composite attachments after aligner placement and removal. Note more attachment failures in flowable (7.5× magnification, bar: 5mm)

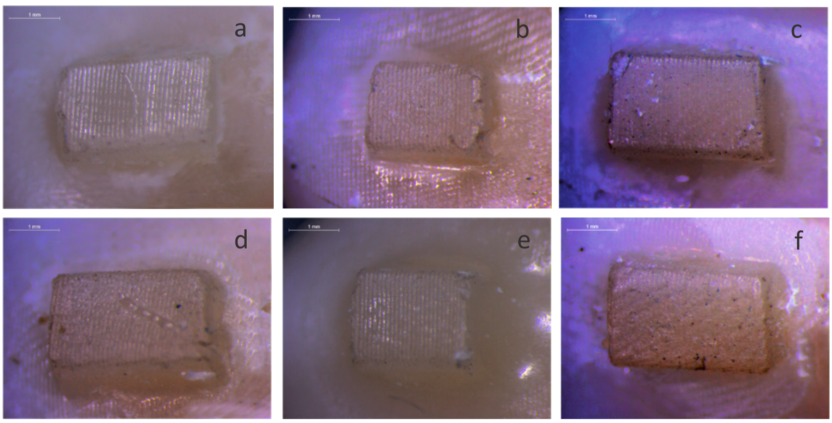

Figure 26. Stereomicroscopic images of zirconia frames with sculptable composite attachments (Group I) after aligner placement and removal. Note central surface scratches (a, d), marginal defects (b, e) and pronounced surface abrasion with loss of the characteristic surface texture (c, f). Right part of images: cervical region, left part: incisal region (25× magnification, bar: 1 mm).

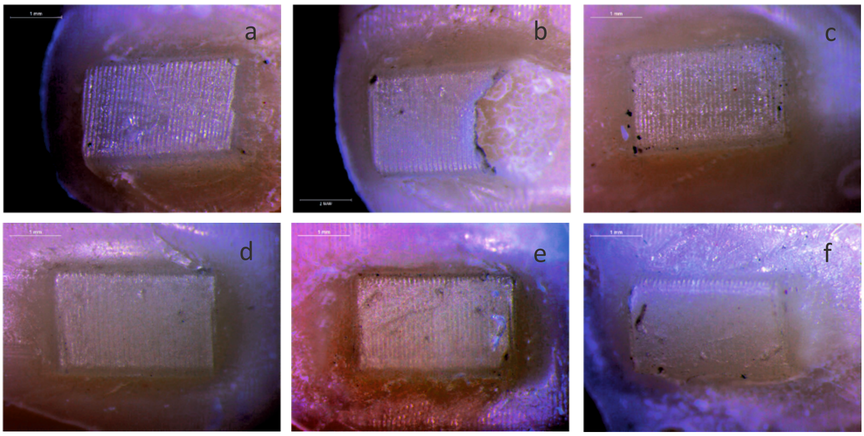

Figure 27. Stereomicroscopic images of zirconia frames with flowable composite attachments (Group II) after aligner placement and removal. Note central surface scratches (a, c, e, f), marginal defects (a, d, e, f), pronounced surface abrasion with loss of the characteristic surface texture (d, f) and bulk fractures (b). Right part of images: cervical region, left part: incisal region (25× magnification, bar: 1mm).

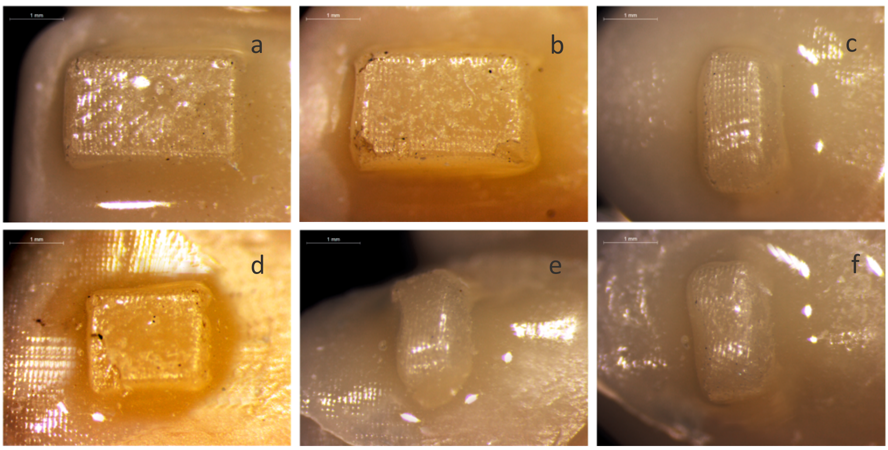

Figure 28. Stereomicroscopic images of zirconia frames with sculptable (Group I, upper row) and flowable (Group II, lower row) composite attachments of the control groups. In both groups the labial surfaces show the characteristic texturing, with minor marginal defects (25× magnification, bar: 1mm).

3D-profilometric images of the regions used for roughness measurements are exhibited in Figures 29-32. The surfaces of the reference group of the sculptable composite attachments (Group I-control, Figure 29), demonstrated mild porosity (a, d) and protruding ridges corresponding to the texturing of the aligner surfaces facing the teeth (b). In few specimens severe porosity was identified at the central part of the attachments, associated with the texturing protrusions. After removal and reseating of the aligners (Group I, Figure 30), the sculptable composite surfaces exhibited well-defined protrusions attributed to aligner texturing, with evidence of abrasive wear and cracks. In some specimens deep abrasion tracks were located at the valleys and severely worn areas at the protruding composite ridges.

For the reference group of the flowable composite attachments (Group II-control, Figure 31), the patterns observed included smooth surfaces, surfaces with mild porosity allocated in line with mild texturing traces and a few cases of severe porosity and parallel fissures associated with the aligner texturing. After removal and reseating of the aligners (Group II, Figure 32), the flowable composite surfaces demonstrated excessive texturing protrusions with abraded peak ridges, cracks and severe abrasion in the valleys. In some specimens a generalized abrasion pattern was observed with pores, that completely modified the original surface profile.

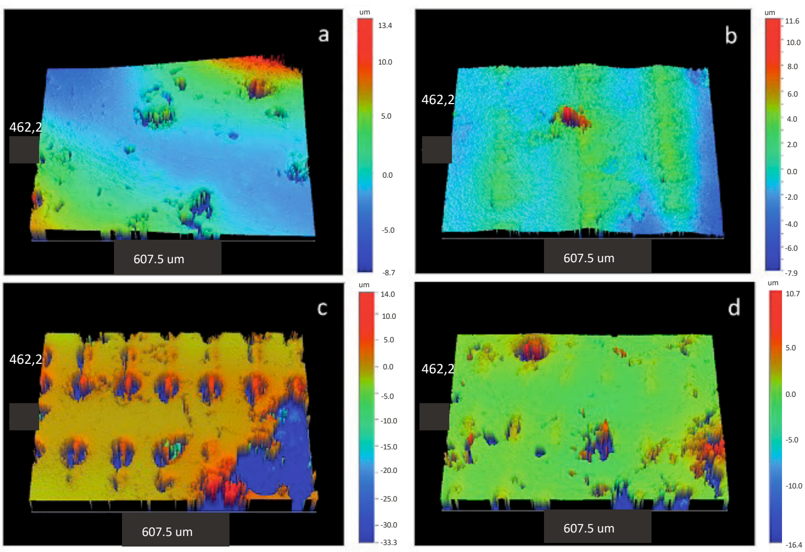

Figure 29. 3D-profilometric images of the reference group of the sculptable composite attachments (Group I-control). The surfaces demonstrate mild porous defects (a, d), appearance of the texturing of the intaglio aligner surface (b) and in some cases severe porosity associated with the texturing protrusions (c) (10× magnification, 462.2 × 607.5 μm^2 analysis area).

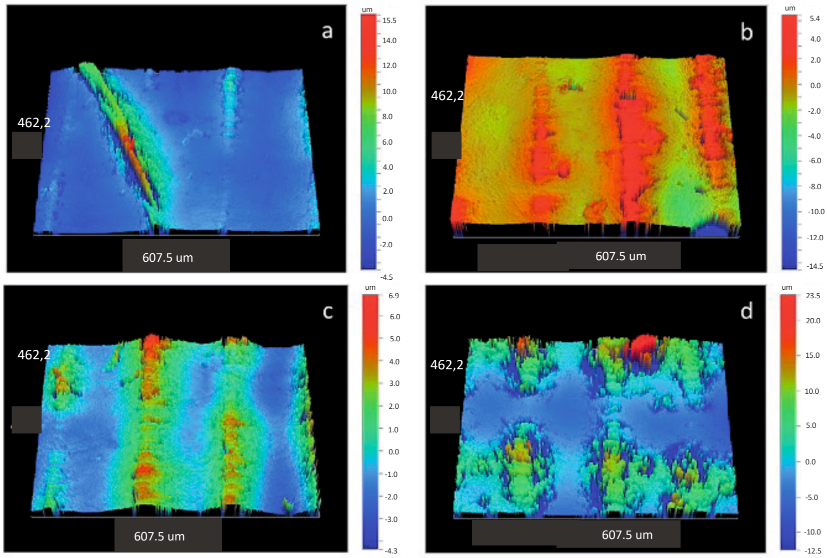

Figure 30. 3D-profilometric images of the group of the sculptable composite attachments after removal and reseating of the aligners (Group I). The surfaces demonstrate intense patterns of the aligner texturing with evidence of abrasive weas (b, c), cracks (a) and intensive abrasion tracks (d) at the texturing protrusions (10× magnification, 462.2 × 607.5 μm² analysis area).

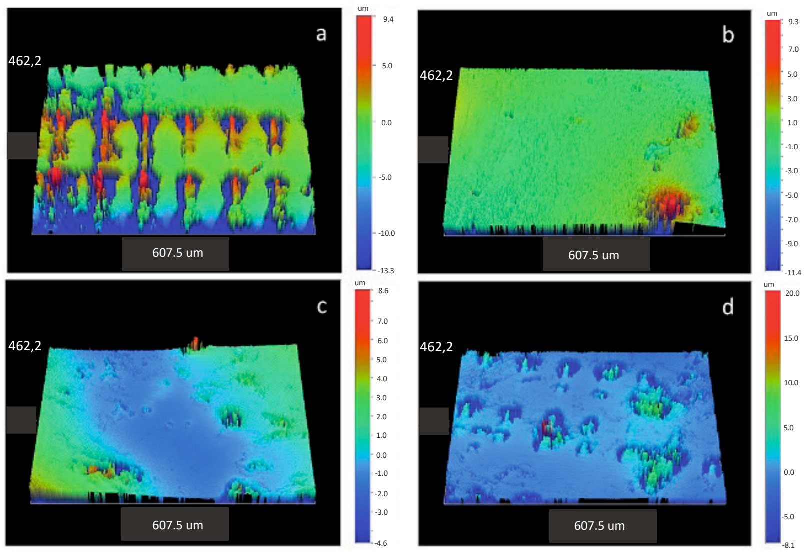

Figure 31. 3D-profilometric images of the reference group of the flowable composite attachments (Group II-control). Some surfaces demonstrate many porous defects and parallel fissures associated with the aligner texturing (a), whereas most were smooth (b, c) or with a mild porosity in line with the texturing (d) (10× magnification, 462.2 × 607.5 μm² analysis area).

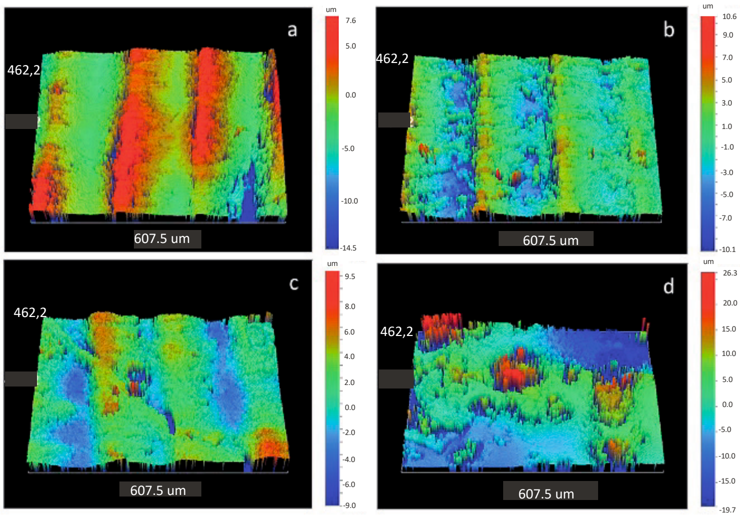

Figure 32. 3D-profilometric images of the flowable composite attachments after removal and reseating of the aligners (Group II). Most specimens demonstrated excessive texturing protrusions with abraded peak ridges and cracks (a), excessive abrasion in the valleys (b, c) and a generalized abrasion pattern with pores, which completely modified the texturing profile (d) (10× magnification, 462.2 × 607.5 μm^2 analysis area).

The results of the roughness parameter measurements are shown in Table 14. There were no statistically significant differences between the control group and the group with removal and reseating of the aligners per material (all comparisons non parametric with Mann-Whitney test, except for Sq, Sz, Sdr, Ssc in sculptable composite and Sdr, Ssc in flowable composite where Student's t-tests were used. Nevertheless, a marginal difference ($p=0.054$) was found in the Sc value in the flowable. Comparisons between the control materials demonstrated a statistically significant difference only in Sds in favor of the flowable ($p=0.041$), all comparisons Student's t-tests). Finally, comparisons between the two materials in the groups after removal and reseating of the aligners, showed a significantly lower Sds value in the sculptable composite group ($p=0.047$, all Mann-Whitney tests).

Table 14. The results of the roughness parameter measurements (means and standard deviations)

GROUP	Sa (μm)	Sq (μm)	Sz (μm)	Sc (μm3/mm2) ×103	Sv (mm3/mm2) ×103	Sdr (%)	Sds (1/mm2)	Ssc (1/mm)
I	2.064 (0.972)	2.747 (1.277)	1.877 (9.023)	3.59 (1.65)	0. 186 (0.081)	6.092 (4.351)	1760.853 (313.977) a	349.32 (123.001)
I Control	1.728 (1.184)	2.4997 (1.444)	18.514 (10.654)	2.45 (1.43)	0.287 (0.267)	3.278 (2.495)	1638.411 (397.592) A	245.168 (99.521)
II	1.973 (1.233)	2.562 (1.571)	17.715 (8.933)	3.14 (1.77)	0.200 (0.177)	5.148 (3.111)	2252.003 (931.144) a	373.42 (81.219)
II Control	1.363 (0.805)	1.7996 (1)	12.089 (4.306)	1.85 (0.951)	0.210 (0.151)	4.133 (2.021)	2119.904 (454.354) A	327.622 (104.81)

Same lowercase letters: Statistically significant differences for comparisons between materials after removal and reseating of aligners (Groups I-II, Mann-Whitney tests for all comparisons).
Same uppercase letters: Statistically significant differences for comparisons between control materials (Groups I Control)-II Control, Student's t-tests for all comparisons).

Full range ATR-FTIR spectra of unset and set specimens along with those subjected to aligner removal and reseating per material are presented in Figure 33. The spectra demonstrate characteristic peak assignments as follows (cm^{-1}): O–H (3442, 1140–1110), N–H (3371), aromatic C..C (3010, 1608, 1595,1510, 830, 801), $CH_3/CH_2/CH$ (2920–2880, 1465–1430, 1370–1360, 720–700), C=O (1715, 1320, 1290), C=C(1634, 1500, 895), CON–H (1540), C–O–C (1260, 1105–1000) and Si–O (1150–1000)[176]. These are the common peaks identified in composites with conventional bispenol-A adducts (i.e., BisGMA, BisEMA, BisPPMA) along with urethane dimethacrulate co-monomers (i.e., UDMA, DUDMA, etc). Based on manufacturer's information the flowable composite used contains in addition a cycloaliphatic monomer and an (β-allyl sulfone) addition fragmentation chain transfer (AFCT) reagent to reduce shrinkage stresses[177]. Some of the set materials of both material groups subjected to the repeated aligner removal and reseating cycles, showed strong peaks of water (3442 and 1642 cm^{-1}), which were not reduced by the conventional drying methods used for all specimens, implying that this water fraction is strongly absorbed.

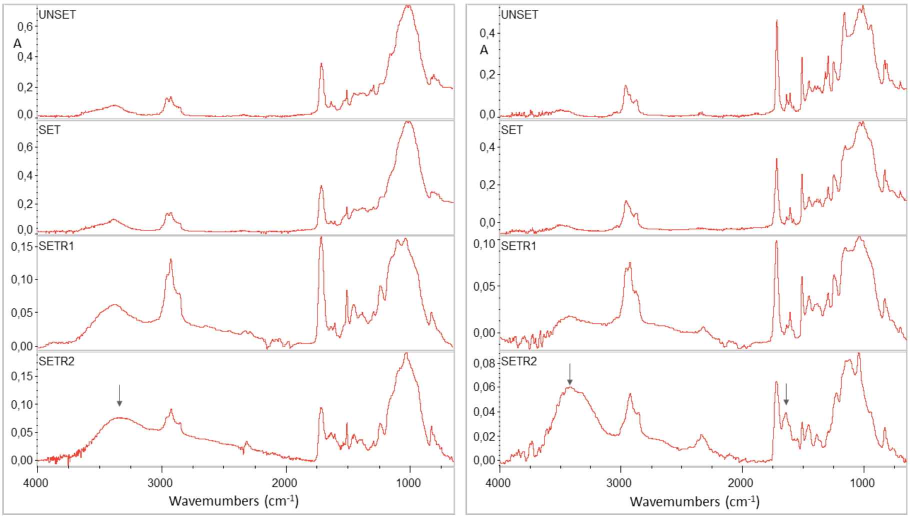

Figure 33. ATR-FTIR spectra of unset and set states of the sculptable (left) and flowable (right) composite materials used as aligner attachments. SETR1 and 2 correspond to specimens subjected to repeated removal and reseating aligner cycles. Arrows show the strong peaks of strongly bound water observed in some specimens (4000-650 cm^{-1} wavenumber range, absorbance scale).

Figure 34 illustrates representative expanded spectra used for calculation of the degree of C=C conversion measurements (DC%), along with the annotation of the analytical and reference bands. Table 15 summarizes the results of DC% for the groups tested. Comparisons between the control group and the group with removal and reseating of the aligners per material, between the control groups and between the material groups with removal and reseating of the aligners showed statistically insignificant differences ($p>0.05$, all Student's t-tests).

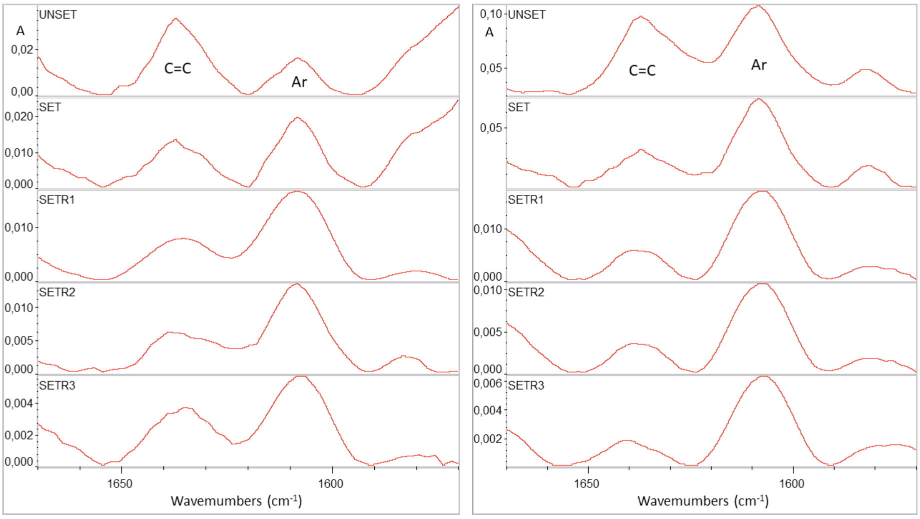

Figure 34. Expanded ATR-FTIR spectra of unset and set states of the sculptable (left) and flowable (right) composite materials used as aligner attachments. SETR1 and 2 correspond to specimens subjected to repeated removal and reseating aligner cycles. C=C, Ar denote the peaks of analytical and reference bands respectively used for calculation of the DC% (1670-1570 cm^{-1} wavenumber range, absorbance scale).

Table 15. The results of DC% measurements (means and standard deviations).

GROUP	DC (%)
I	69.7 (8.8)
I Control	62.6 (1.9)
II	66.2 (4.8)
II Control	61.5 (1.1)

6 DISCUSSION

The accuracy and predictability of orthodontic treatment outcomes with aligners, forces generated during treatment, aligner/attachment interfaces during a simulated orthodontic treatment with aligners as well as the effect of commercial cleansers on aligner composition and mechanical properties were the main topics studied in this thesis. The orthodontic forces exerted by aligners rely on factors such as material thickness, hardness, elastic modulus, and degree of activation[178]. In order to achieve effective and predictable tooth movement with aligners it is essential to preserve their initial mechanical characteristics throughout their clinical use[21].

Forces and moments generated by aligners during orthodontic tooth movement

Although the biology of tooth movement during orthodontic treatment is irrelevant to the appliance choice, a notable difference in biomechanics arises when comparing clear aligners to fixed appliances. This distinction is evident due to differences in positioning and tooth coverage of the aforementioned methods throughout the course of treatment.

Regarding the evidence on forces and moments generated by aligner-type appliances this is the first attempt to systematically evaluate the evidence related to orthodontic tooth movement. To our current knowledge, this marks the initial effort to methodically evaluate the available evidence concerning the forces and moments generated by aligner-type appliances in relation to orthodontic tooth movement. It's evident that only in-vitro studies were included as the basis of evidence. Due to variations across studies in terms of conditions, aligner composition and design, tooth type, and the nature of movement, concrete comparisons between aligner types proved challenging.
Derived from a qualitative synthesis, it became apparent that even aligners as thin as 0.5 mm (such as PET-G aligners), which are among the thinnest available commercially, exerted a notable and non-negligible load on teeth which could potentially have a negative impact to the surrounding periodontal structures in terms of overloading[155]. To achieve a lower initial stiffness, a series of aligners was recommended, including an initial aligner of 0.4 mm thickness, while Invisalign (polyether-urethane, Align Technology) employs an adjunct with a thickness of 0.7 mm[155,157,158]. Furthermore, the ideal force couple required in order to achieve bodily movement and torque could not be established using

standard plain aligners. This has led to the proposal of modifications like attachments, divots, and cuts with the intent to facilitate the desired tooth movement[28,162,163]. Notably, aligners made with Biolon (Polyethylene terephthalate glycol PET-G, Dreve Dentamid GmbH) material yielded higher forced and moments when compared to Erkodur (Polyethylene terephthalate glycol PET-G, Erkodent), although statistically significant differences were observed only within specific experimental conditions. The dissimilarities in the mechanical performance observed between Biolon and Erkodur appliances may be attributed to deformations arising at the contact regions during the thermoforming process, friction-related phenomena, as well as the characteristics of the polymer material[17,162]. The former appliances undergo thermoforming under a pressure of 6 bars pressure, while the latter are vacuum-formed under 0.8 bars of pressure[162]. Furthermore, according to the manufacturer's guidelines, a spacing foil of 0.05 mm is positioned between the tooth and the appliance during the thermoforming procedure of Erkodur appliances[17,162]. Although it is possible for this foil to experience some degree of post-thermoforming shrinkage, it is reasonable to assume that the its final thickness could be comparable to that of a single activation step.

In terms of moment to force ratio, the quantitative analysis did not demonstrate a distinct disparity between the thinnest commercially available aligners at 0.5 mm and their counterparts measuring either of 0.625 mm or 0.75 mm. Although thicker materials may possess higher levels of rigidity, this doesn't essentially anticipate to increased levels of effectively exerted forces a fact that may lead to clinical implications. The suitability of the intermediate stage thickness of these adjuncts, such as 0.625 mm, has been brought into question, and it might even be deemed unnecessary within the clinical context[156]. This stands in contrast to the existing recommendations, which advocate for the use of three consecutive aligners with progressively increasing thicknesses[179]. In a study conducted by Elkholy et al.[15], the authors aimed to uncover potential evidence of translational palatal movement of the central incisor, nonetheless this was not achieved since the final exerted forces led predominantly to tipping adjustments. Moreover, the identified outcomes were based on aligners possessing a gingival edge width of 3-4 mm.

Laboratory-based studies conducted in controlled conditions can effectively simulate the initial mechanics of tooth movement. Consequently, the levels of forces or moments reported in these studies represent the maximum values that could be generated overall. Thermoplastic aligners experience a reduction in force over a span of two weeks, ranging from 50% of the initial strength[20] to a five-fold decrease[179]. The process of tooth movement is influenced by the interaction of exerted forces and moments. Therefore, the "moment to force ratio" emerges as the most suitable metric to accurately portray simulated tooth movement conditions, applicable to both tipping and translational movements, regardless of the expected magnitude of the movement. However, the width of the aligner's gingival edge has been identified as a significant factor that predicts the initial forces/moments generated by the aligners. Notably, intrusive movements seem to be more susceptible to the configuration of edge width compared to tipping movements, with aligners lacking distinct edges being linked to lower force levels[156].

The current systematic review was pre-registered with a predetermined protocol and followed a transparent methodology in terms of reported parameters and outcomes. A comprehensive search strategy encompassing seven databases, including both published and unpublished literature, was implemented to minimize potential publication bias. The reporting of the included studies exhibited an overall positive quality, enabling a thorough evaluation of risk of bias within studies. In broad terms, there is a need to focus on enhancing laboratory conditions to ensure that researchers can maintain blinding whenever possible during the evaluation of various aligner types in relation to biomechanical aspects. In addition, it is important to acknowledge that while the risk of selectively reporting outcomes was minimal due to the proper matching of variables in the methodology and results sections, no study evaluated was pre-registered or provided a published protocol. However, the review does have certain limitations. Firstly, the quantitative synthesis drew from only two studies, focusing on a very specific form of tooth movement involving the upper central maxillary incisor. These studies exhibited a high degree of heterogeneity, thereby limiting the generalizability of findings to a narrow spectrum of interactions between materials and teeth. Secondly, the data collected derived from laboratory simulation conditions and cannot be directly extrapolated to the biological mechanisms of tooth movement within the periodontal ligament. Furthermore, the biomechanics of tooth movement were studied within the included research solely within the context of individual teeth, disregarding neighbouring teeth, the elastic modulus of the ligament, occlusal/mastication forces, or considerations related to soft tissue. Lastly, in-vitro studies are susceptible to inherent bias due to the lack of standardized procedures for determining desired effects. Typically, specific measurement devices connected to tooth models secured to sensors and adhering to a coordinate system that allows for tooth mobility and simulation of the periodontal ligament were utilized. Any variations in the described laboratory setup across different studies could lead to disparate outcomes. Given these factors, and in accordance with clinical research guidelines, there is a pronounced necessity for the formulation of consistent study protocols prior to commencement, as well as a consensus on experimental settings and universally applicable core outcome sets, as recommended[180].

Treatment outcome with orthodontic aligners and fixed appliances

Evidence from randomized trials and matched non-randomized studies on treatment outcome with orthodontic aligners or braces was systematically evaluated. Among the initial 1376 records identified through the literature search, a total of 11 trials (encompassing 887 patients) were eventually included.

Comprehensive findings from meta-analyses incorporating overall ABO-OGS scores, individual ABO-OGS components, and the proportion of treated cases achieving an 'acceptable' finishing quality (ABO-OGS score < 30) strongly indicate that treatment outcomes are less favourable with aligners in comparison to braces (refer to Table 7). Prior research has highlighted the notable challenge of controlling root movement using aligners, particularly in the absence of attachments [166,168,181]. The process of root movement could potentially benefit from the incorporation of ellipsoid precision attachments capable of generating couples[181], although this remains an aspect that requires further research. Conversely, three ABO-OGS components (alignment, marginal ridges, and interproximal contacts) yielded highly similar results for both treatment modalities. This correspondence is expected, as aligners are recognized for consistently achieving effective space closure of up to 6 mm through gradual tooth tipping and are adept at straightening dental arches by derotating teeth, especially when coupled with composite attachments.[135,166,182]

Conversely, the PAR index demonstrated, no substantial differences overall between aligners and braces, except for a significant divergence in PAR reduction (p=0.06; refer to Table 7) and notable variations in the PAR components for upper anterior teeth and overbite that favoured braces. This contrast in outcomes between the ABO-OGS and the PAR index can be attributed to fundamental dissimilarities between the components of these two assessment tools. The PAR index was devised to systematically evaluate the outcomes of orthodontic treatment, aiming to be applicable in both the assessment of orthodontic care quality and scientific research. Nonetheless, it offers a broad appraisal of occlusion while disregarding elements such as tooth inclination, remaining spaces, and alignment of the posterior dental arch, significant variables in cases intended for board examinations[139]. Moreover, it does not provide the intricate assessment of tooth relationships within an ideal dental arch, as achieved by the ABO-OGS. The latter was designed to meticulously evaluate the details anticipated in a finely completed case across all three planes.

Reported limitations of the PAR index[183] include, among others, low weighting for overbite scores and substantial weighting for overjet scores[184]. Indeed, post-treatment PAR scores do not significantly correlate with post-treatment ABO-OGS scores[185,186]. The PAR index has also been employed extensively to gauge the initial severity of a case. However, the PAR index fails to include factors like skeletal discrepancies/cephalometric values, developmental tooth anomalies, ectopic teeth, or relationships involving soft tissues. For these reasons it does not exhibit strong correlation with the ABO DI[185].

When considering orthodontic treatment outcomes, it becomes evident that the proficiency of the clinician has a notable impact not only to the choice of the most suitable treatment modality but also to the administered quality of treatment. Consequently, future research endeavours should not only focus on conducting high-quality randomized trials that can alleviate biases arising from factors external to the operator, such as patients' clinical characteristics or levels of response/compliance, but should also aim to investigate the influence of varying levels of clinician expertise on the observed treatment outcomes. As far as treatment duration is concerned, performing a comprehensive data synthesis using either aligners or braces proved challenging due to the emergence of a highly heterogeneous image (refer to Figure 19). There are studies that favour one appliance over the other, showing notable variations, while other studies indicate no substantial differences (Figure 19). Hence, it's reasonable to infer that the selection of the appliance alone is insufficient to significantly determine treatment duration. It becomes necessary to meticulously consider other factors in future research, such as baseline case severity, extraction procedures, aligner quantity, refinements utilized, and the established standard of care under which patients are treated.

Regarding the adverse effects of treatment, a single study addressing External Apical Root Resorption (EARR)[168] demonstrated a notably lower percentage of root resorption in incisors during treatment with aligners compared to braces. It is important to emphasize here that evaluating EARR during treatment is intricate, as various risk factors contribute, including the patient's inherent genetic susceptibility to EARR[187], the selected mechanotherapy[188], treatment duration[189], and the extent of tooth movement[187]. A thoroughly conducted study, which meticulously accounted for confounding factors like baseline severity according to ABO DI, genetic variations, and absolute apical displacement, concluded that treatment involving orthodontic aligners leads to similar levels of EARR as fixed appliances[187]. Hence, it could be wise to investigate whether any notable variations in reported EARR within the literature might stem from teeth being subjected to comparatively lesser movement with aligners.

Moreover, another individual study revealed no substantial discrepancy in the occurrence of gingival recessions two years after treatment with aligners compared to fixed appliances ($p=0.86$)[170]. It can be anticipated that the choice of appliance alone may not directly influence the development of gingival recession. Even if the choice of appliance was linked to increased anterior anchorage loss or incisor proclination (which was not observed), this wouldn't necessarily result in a higher risk of gingival recession[190,191]. While, on average, orthodontic treatment does elevate the risk of gingival recessions[192], the precise causative factors are multifaceted, encompassing risks such as periodontal disease, mechanical trauma, patient age, smoking, and the creation of bone dehiscences due to positioning teeth beyond the bounds of the alveolar plate[191, 193].

Lastly, a single study[165] offered limited evidence regarding the impact of appliance choice on the loss of periodontal attachment. This study focused on adults with a history of treated periodontal disease and assessed the orthodontic alignment of anterior teeth. Upon obtaining raw data from the author and aligning the baseline status of the groups, no disparities were observed between aligners and fixed appliances in terms of periodontal probing depth ($p=1.00$) or alveolar bone levels ($p=0.69$). Conversely, fixed appliances demonstrated significantly quicker repositioning of migrated anterior teeth in patients compared to aligners (3.9 versus 6.0 months; $p=0.01$). It is worth noting here that while previous systematic reviews, primarily drawing from studies with methodological limitations, have suggested that aligners could be linked to better oral hygiene compared to fixed appliances[10,194,98], a recent Randomized Controlled Trial (RCT)[61] found no consistent or significant advantage in terms of plaque index, gingival index, or periodontal bleeding index between patients treated with aligners and those treated with fixed appliances. Consequently, it is evident that proper oral hygiene can also be maintained with fixed appliances.

The systematic review, from which the evidence is derived, possesses several strengths consisting of a pre-registered protocol[195], a thorough and extensive literature search, inclusion of both randomized and matched non-randomized studies, application of contemporary analytic methods[143], utilization of the GRADE approach[146], and the transparent presentation of all gathered data[196].

Nevertheless, certain limitations are present in the current review. Methodological concerns are evident in all the included studies which may potentially influence conclusions. This is particularly notable in the case of the incorporated retrospective non-randomized studies[9,197]. The possibility of selection bias cannot be completely dismissed when non-randomized designs are employed. To mitigate this potential limitation arising from group dissimilarity in comparative studies, studies with populations matched for baseline characteristics were specifically selected. Incorporating non-randomized studies into meta-analysis is not considered prohibitory, provided robust assessment of biases has been conducted. Recent guidance also provides direction on appropriately integrating such study designs[147]. Additionally, a diverse range of outcomes emerged across studies, reflecting the expected variation due to the diverse array of malocclusions, appliances, and clinical contexts considered. This heterogeneity, though, primarily impacted the magnitude of effects rather than their direction, except for treatment duration, where a consistent effect of appliance choice was not observed. Moreover, the majority of meta-analyses were predominantly founded on small trials, potentially influencing the precision of estimates[198]. Furthermore, the limited number of trials ultimately included in the meta-analyses, combined with their incomplete reporting of outcomes and potential confounding variables like case severity, oral hygiene, compliance, use of bonded attachments, number of aligners, necessity for refinements, or the extent of interproximal enamel reduction, prevented the execution of numerous subgroup analyses and meta-regressions that could facilitate the identification of patient groups where aligners might be an equivalent or even more suitable treatment option compared to fixed appliances.

Accuracy of clear aligners

No significant disparities were identified between predicted and achieved movements in the horizontal plane. The most pronounced divergence was noted in the alteration of maxillary intercanine width. This outcome isn't unexpected, considering that maxillary canines possess long roots and conical crown shapes with minimal undercuts to improve aligner grip. Expansion between premolars was accurately achieved, yet the average amount of planned expansion was modest, measuring only 1.49 mm for maxillary premolars and 1.76 mm for mandibular premolars.

The most noteworthy variations were observed in vertical movements[100]. Particularly, intrusion was the most unpredictable movement, with linear movements differing by a range of 0.8 to 1.5 mm. Notably, for the maxillary central and lateral incisors, even when the intended movement was intrusion, the accomplished movement was extrusion. This could be attributed to the method of superimposition. Aligner use results in a bite-block effect due to the placement of two 0.38 mm thick aligners between posterior teeth throughout the treatment. If unexpected intrusion of molars occurs, the superimposition process could lead to the appearance of incisor extrusion on post-treatment models. Another observation that supports this theory is that the achieved extrusion often exceeded predictions, although the difference was not statistically significant.

Although the occurrence of extrusion instead of intrusion might be perceived as a limitation of this study, this finding should not be dismissed. The extrusion of incisors in relation to molars could hold clinical significance. The bite-block effect could potentially render deep bites more challenging while making open bite cases more amenable to aligner treatment. Notably, this study incorporated three patients with anterior open bite, one patient with posterior open bite, and multiple patients with deep bites. Future investigations could opt to focus solely on one of these malocclusions to yield more definitive insights into the vertical effects of aligner treatment. The utilization of anterior bite ramps (Figure 35) could counteract the bite-block effect; however, only two patients in this sample received this intervention. This aspect of Invisalign's functionality might have a noteworthy impact on correcting deep bites and is worth studying separately.

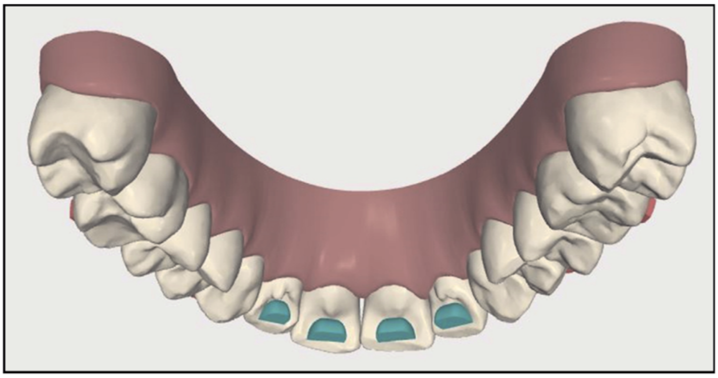

Figure 35. Bite ramps are projections of the aligners on the lingual surfaces of the maxillary incisors that disclude the posterior teeth (screenshot from ClinCheck).

All achieved rotations were consistently smaller than the predicted values, exhibiting varying degrees of discrepancy. The median differences ranged from 0.9 to 3.05 degrees. Similar findings were observed by Kravitz et al.[135], who identified that rotations of both the maxillary and mandibular canines were the most unpredictable among all anterior teeth. They suggested that overcorrection might serve as a solution for this issue, but only up to a certain extent. An excessive overcorrection could resemble a bend on an archwire that's too robust to be inserted into the bracket slot. Additionally, overcorrections are not as simple for other types of movement, like horizontal and vertical adjustments. One should always consider the potential side effects and occlusal interferences associated with such overcorrections.

While many preceding studies have presented the accuracy of aligners in terms of percentages, in this study a different approach has been adopted by concentrating on the magnitude of disparities between predicted and achieved movements. This decision was primarily driven by the fact that percentages offer fewer comprehensive insights into the specific movements studied and the identified differences. It is worth mentioning that all previous investigations were conducted before the introduction of the SmartTrack material, the latest attachments, and software updates[135,166,182,199,200]. With this study, it was aimed to provide valuable evidence concerning the accuracy of the current version of Invisalign.

At this point, it is essential to acknowledge certain limitations. The retrospective nature of the study introduced the potential for selection bias, which was challenging to entirely mitigate. Participants were treated with aligners (Invisalign, Align Technology) based on the decision of a highly skilled practitioner. However, the fact that refinements were needed towards the end of treatment suggests that treatment was somewhat unsuccessful, so the outcomes might not be applicable to all patients treated with aligners. Furthermore, it should be noted that retrospective studies may struggle to control patient cooperation[135]. Yet, reviewing patient records at the end of treatment to verify adherence to regular aligner changes and appointment attendance seems to be a comparably effective approach to the compliance logs employed in other research studies.

In addition, superimpositions were conducted on posterior teeth, which were considered stable despite minimal observed movement. This approach was chosen as the most viable option due to the absence of stable anatomic structures in ClinCheck. To address the challenge of superimposition, cone-beam computed tomography could offer a partial solution. If such scans were attainable at both time intervals, cranial-base superimposition would provide an accurate means of measuring accomplished movements since it demonstrates minimal changes after neural growth is completed[201]. However, for anticipated movements, measurements would still necessitate the use of ClinCheck. Attachments and interproximal reduction could potentially influence the precision of different tooth movements, although the available evidence is inconclusive[28, 166, 200]. In this study, it was presumed that the overseeing orthodontist possessed adequate expertise to make appropriate decisions regarding their usage, and no limitations were imposed in this regard. Furthermore, all measurements were done at the incisal edges. Buccolingual and mesiodistal tipping and torque were not studied. There's a possibility that the actual movements deviated from the predicted ones (for instance, more tipping than translation), which could have implications for the displacement of the incisal edge.

Finally, a significant limitation of this study, as well as other studies with similar designs conducted thus far, is that multiple teeth were analysed within the same patient. In reality, the movement of one tooth isn't isolated from the movement of neighbouring teeth or those used as anchorage. Moreover, the different components of tooth movement across various planes were examined separately, although each tooth undergoes just one resultant movement. The most optimal approach to address this limitation would involve including only one movement of a single tooth from each patient. However, this would require an exceptionally large sample size or a reduction in variables. In the realm of future research, it would be advantageous to narrow down the number of variables measured while increasing the sample size. This approach would likely yield more dependable outcomes.

Effect of cleansers on orthodontic aligners in-vitro

The orthodontic force exerted by aligners relies on factors such as material thickness, hardness, elastic modulus, and the degree of activation[178]. For effective and predictable tooth movement, the mechanical characteristics of aligners must remain stable during their use[21]. Nevertheless, aligners encounter not only the oral environment but are also subjected to disinfection and cleaning solutions for hygiene purposes[40,50,56,202,203]. The outcomes of this study revealed that certain cleaning agents might influence the mechanical attributes and/or surface chemistry of aligner materials crafted from polyethylene terephthalate glycol (PET-G) or poly(ester–urethane).

The examined cleaners have been specifically formulated for use with orthodontic aligners, although the quantitative composition of certain products (RB, RC resembles conventional denture-based cleaners[204]. These cleaners, RB and RC cleaners, predominantly comprise of sodium perborate or sodium percarbonate, which, when dissolved in water, break down into borates and hydrogen peroxide or hydrogen peroxide along with sodium and carbonate ions. Hydrogen peroxide further decomposes into active oxygen and water, while carbonates convert into carbon dioxide and water[205]. These cleaners encompass surfactants, flavouring agents, and pigments. It is established that cleaners within this category, often referred to as alkaline peroxides, can diminish the hardness and flexural strength while increasing the roughness of polymethyl methacrylate denture-base materials. This effect arises due to hydrolytic oxidation and network plasticization, involving the extraction of residual methyl methacrylate monomer, cross-linkers, oxidation by-products, and more[206, 207]. Concerning ST, the composition given does not entail a source of active oxygen like the other two cleaners; the primary difference lies in its lower pH. All the cleaners incorporate EDTA chelators, with tetrasodium salt of EDTA known for its inhibition of biofilm formation[208]. Disodium EDTA exhibits enhanced solubility in water and a more rapid chelation effect[209]. Additionally, pyrophosphates and polyphosphates are included as agents to inhibit the precipitation of calcium and magnesium on the appliances[210, 211]. No significant differences were observed in the mechanical properties of Invisalign aligners following immersion in any of the three cleaning solutions, as compared to the control group. This suggests that the poly(ester-urethane) structure of Invisalign remained stable against the degradative impacts of the tested cleaners. However, for Clear Aligner, a significant decrease in Martens Hardness and elastic index was evident, indicating that these aligners experienced a softening and increased brittleness regardless of the active ingredients and pH levels of the cleaners used. One plausible explanation is the heightened hydrolytic instability of the esterified hydrophilic polyglycol segments within the amorphous PET-G. A notable finding of the study was the distinct effects of RB and RC cleaners on R_{IT}, which relates to the aligner materials' behaviour under creep. RC, sharing the same pH as RB, had a milder impact on Clear Aligner, similar to the control group. In contrast, RB exhibited significantly higher R_{IT} values than RC, resembling the impact of the acidic ST. This could suggest that factors beyond pH might contribute to the hydrolytic degradation. In industrial applications, sodium percarbonate is recognized to be more reactive than sodium perborate, with the latter often requiring additional alkalinity (usually via 1% NaOH solutions) to achieve effective bleaching[212]. Whether a similar mechanism is operative in RB remains unclear and could explain the observed difference. Furthermore, an aspect that might influence the mechanical properties of aligners is the role of residual stresses generated during the manufacturing process[49]. Successive immersions could induce relaxation, potentially affecting the measured mechanical properties[49]. However, the extent and orientation of residual stresses in orthodontic retainers remain uncertain. This could present an interesting topic for future research.

To examine the chemical modifications occurring on the aligner surfaces, an ATR-FTIR analysis was employed. While the technique's sampling depth is confined to the topmost 2 μm layer (as opposed to the comprehensive analysis of ground/polished specimens using IIT), it has the potential to offer crucial insights into the mechanisms of degradation at play. When examining the spectra in the fingerprint range (2000–650 cm^{-1}), notable differences were observed only in Clear Aligner treated with ST, where a peak emerged at 1699 cm^{-1} attributed to acid production through the oxidation of the PET structure[173]. Through a more detailed analysis involving curve-fitting of ester peak components, it was discovered that there was a presence of free and hydrogen-bonded C=O groups in a ratio of 0.4 for RB, RC, and 0.5 for CO and ST. The slight reduction observed following treatment with alkaline peroxides (RB, RC) might indicate the degradation of a small fraction of free-ester groups. Peaks found at the highest (1743 cm^{-1}) and lowest (1693 cm^{-1}) wavenumbers, common across all groups, suggest the presence of oxidized impurities in the control samples, which were diminished after treatments, particularly at the highest wavenumber. Two additional peaks, resolved at 1677 and 1644 cm^{-1}, imply that the acid generated may exist in multiple forms (terephthalic, glycolic, etc.). Considering the depth limitations of both ATR and IIT methods, it can be inferred that the chemical changes may extend up to the depth of the IIT method, thereby affecting mechanical properties accordingly. A more detailed curve-fitting analysis of ester peak components offered intriguing insights for Invisalign, where the mechanical properties were unaffected by any of the cleaners, as indicated by the spectra in the fingerprint range. After RB treatment, weak peaks at the highest (1740 cm^{-1}) and lowest (1672 cm^{-1}) wavenumbers appeared, signifying oxidative effects. Furthermore, the peak at 1687 cm^{-1}, associated with the low-ordered crystallinity of the urethane segment, was heightened at the expense of the corresponding amorphous peak (1699 cm^{-1}). This could indicate an early development of a more brittle structure, potentially linked to aging. This phenomenon was unique to treatment with one alkaline peroxide (RB), suggesting that the poly(ester-urethane) structure might be more sensitive to this type of cleaner, and that RB is a stronger alkaline peroxide than RC. Although the chemical changes in Invisalign didn't correlate with the mechanical response, they effectively demonstrate the capacity of ATR-FTIR spectroscopy to identify initial degradative shifts in the surface chemistry of the aligners.

The above results should be interpreted cautiously as the aligners were not exposed to intraoral conditions, which would be necessary to accurately assess the extent of degradation induced by cleaners in real-time intraoral settings. While changes observed through simple immersion tests provide insight, they could potentially lead to premature deterioration of aligner properties, possibly affecting their lifespan during actual use. To gain deeper insights, further research incorporating in vivo functional loading as a testing factor could shed light on the impact of cleansers on aligner properties and help determine when mechanical deterioration begins in these thermoformed materials.

Surface alterations of resin composite attachments induced by orthodontic aligners

The results of the present unpublished experimental study showed that there were no statistically significant differences in the roughness parameters and DC% between the control and the group of attachments after removal and reseating, for the sculptable and flowable composites respectively. Statistically significant differences were found only in Sds when comparisons were made between the two materials for the control or the removal and reseating states.

The materials selected were a sculptable universal and a flowable universal restoratives, which are the types of the composites used for aligner attachments. These materials are based in similar monomer systems (BisGMA, BisEMA, UDMA) with the addition of dicyclodecane dimethanol dimethacrylate (DCDDMA) in the later. The sculptable composite demonstrates higher viscosity and a "putty" consistency, whereas the second is a thixotropic flowable. The sculptable has a higher filler content (75-76w%, 53-55% v%) than the flowable (68.2 w%, 46.4 v%) and better mechanical properties. Although in previous studies high loaded sculptable materials were used[213, 214] for aligner attachments, currently several manufacturers have introduced flowable materials. The main reason is the improved rheological characteristics of the flowables, which could facilitate easy and porous-free resin penetration into the attachment frame of the aligners and contact with tooth surfaces. For this issue the putty consistency of sculptable composites may increase porosity when applied in the box-shaped inclusions of the aligners due to inclusion of air. Moreover, the reduced wettability of sculptables on tooth surfaces may further promote porosity at the tooth-attachment interface.

In the present study the substrates used for bonding the attachments were Zirconia (3Y-TZP) arches. The reason for the selection of this material was that the original design of the study included the assessment of the water eluents from the composite attachments, which currently is in the final stage of measurements employing liquid chromatography and mass spectrometry (LC-MS). The selection of zirconia arches was based on the water insolubility, absence of release of interfering compound in the LC-MS measurements, dimensional stability in water and the bonding capacity of the composite attachments. The zirconia surfaces were sandblasted with 50 μm alumina with an intraoral sandblaster at low-pressure and treated with a universal primer containing two phosphate monomers (10-MDP, MDTP). The use of alumina blasting with phosphate-monomer containing primers has been widely accepted as an efficient treatment method of the intaglio surfaces of zirconia crowns for strong and durable bonding with composite luting agents, by combining micromechanical retention and chemical adhesion [215,216]. The study was limited to one week period to provide information on the early changes induced in the attachments after bonding and aligner placement, within the effective service period of an aligner. This initial in-service period is the most important since the attachments are not matured in terms of polymerization and are directly exposed in the water along with the extra-coronal forces induced by the aligner, which produce an abrasive effect on the original material morphology and topography. Note that a week of water immersion is considered as a conventional water absorption equilibration period, where remaining monomer and early oxidative compounds of pendant C=C bonds are released[217]. The rate of these phenomena is usually reduced with time, especially when the abraded attachments loose conformity with the aligners and thus the aligner-attachment interfacial friction is reduced [213].

The stereomicroscopic and the optical profilometric roughness measurements were performed on attachments bonded to the frames, to avoid debonding induced defects. The stereomicroscopic assessment of the morphological features of the control groups demonstrated a few problems in integrity of the buccal angles of the sculptable material, possibly assigned to air inclusion. Moreover, there was evidence of surface porosity and loss of the characteristic surface texture of the intaglio aligner surface in some specimens, which may indicate inadequate wettability of the aligner by the sculptable composite. Due to the better wettability of the aligner surfaces, such defects were limited in the flowable, although still some evidence of labial surface defects were registered. In the groups subjected to the repeated cycles of attachment loading, after aligner removal and reseating, the attachment surfaces exhibited abrasion-induced morphological changes, such as cracks, angle rounding, loss of surface texturing and some cases of bulk fractures. Scratches and bulk fractures were more frequently observed in the flowable composite, a finding mainly attributed to the lower mechanical properties of this material. An interesting finding was the increased debonding percentage found in the flowable group. More than half of this percentage was associated with debonding during the first removal of the aligner, with the attachment locked inside the aligner frame. Two possible reasons may be implicated with this phenomenon; first the higher wettability of the aligner by the flowable material and second the higher mechanical retention of the flowable with the textured surface due to the higher volumetric shrinkage of the flowable from the composite (1.83 vs 3.21%[218,219]) within a complex three-dimensional retentive structure than the tooth surface. It should be noted that in the present study the bonding treatments to zirconia were the same, for materials with small differences in the monomer content and that the specific flowable material was selected based on the manufacturer's claim for low shrinkage. Although the clinical relevance of this finding is unknown, it may indicate a potential limitation of the currently available flowable composite materials as aligner attachments. Nevertheless, sculptable composites may demonstrate application problems in very small aligner cavities. A hydrophobic low-flow consistency materials could present handling advantages in such cases. The roughness analysis was used to quantify the topographic differences between the control specimens and the specimens after aligner removal and reseating. Amplitude, hybrid and functional parameters were selected for better characterization of the surfaces. From all these parameter Sdr and Ssc are considered as of major importance to characterize how surfaces interact when the one is moved against the other, how friction is implicated and how they will abrade due to the contact. These two parameters focus on the actual contact area due to the presence of surface summits than the entire area and can be used to predict the mode of surface deformation under load, the friction and wear characteristics of a surface[220]. The data used for roughness parameters were unfiltered incorporating the waveness pattern of the attachments produced by the intaglio aligner surface texturing (Figure 36). The 3D-profilometric images obtained at 10× nominal magnification of the Mirau lens were more than twice the magnification of the stereomicroscope, with each image representing the most affected zone. The porosity observed in the control groups was more pronounced in the sculptable composite. This is in accordance with the wetting problems and the air inclusion found also in the stereomicroscopic images. However, in few cases of both control groups, excessive porosity aligned with texturing traces was observed, with more intense characteristics in the flowable material. A possible explanation is inadequate wetting at the region with inclusion of air voids (spherical, ellipsoid), which after setting created larger defects in the flowable material, due to its higher shrinkage. After aligner removal and reseating the sculptable material presented various degrees of abrasion of the protruding regions. In some cases of the flowable material a generalized surface wear was observed by completely removing the parent morphological features of the control group, suggesting a more severe effect. The high variances in the topography resulted in statistically insignificant values between all paired comparisons (control attachments vs attachments after aligner removal and replacement for both materials), with a marginal difference found only in the flowable for Sds ($p=0.054$). This may indicate that the number of protruding summits were reduced per surface area after aligner removal and reseating. Comparison between the control materials and the materials after aligner replacement and reseating, clearly demonstrated a significantly higher Sds for the flowable. This finding corroborates the improved rheological properties of the flowable, which may penetrate more efficiently into the texturing details of the aligner surfaces facing the teeth.

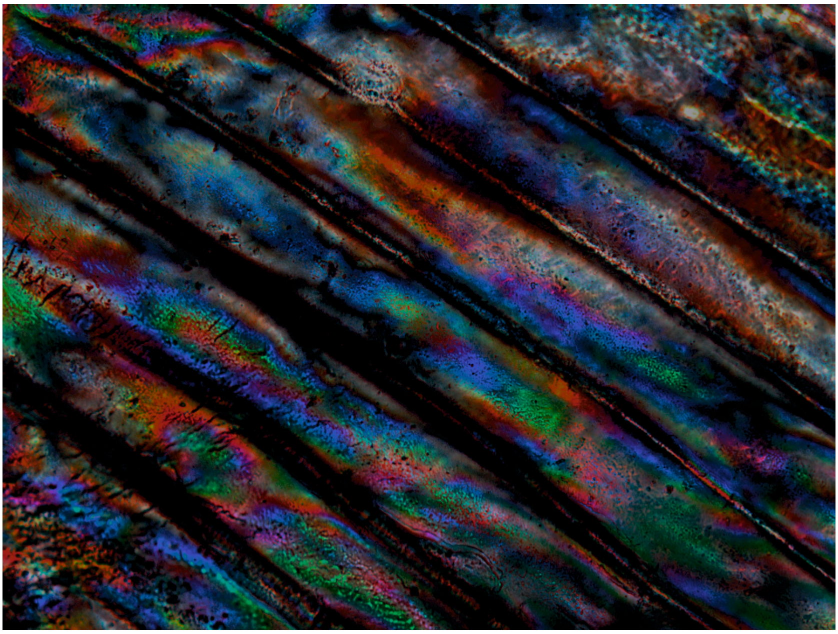

Figure 36. Reflected polarized light image of the inner surface of the aligner, with the characteristic texturing.

The analysis of the composition was mainly limited to the organic part of the composites, since the organic compounds released are mainly associated with possible side effects. The ATR-FTIR spectroscopic analysis probed the superficial 2 μm zone of the materials, which is within the range of the Sa values of all the groups tested. The spectra of the materials after control and aligner removal/reseating demonstrated similar peaks, indicating no evidence of hydrolytic changes. This may be explained by the short water-immersion period and the limited removal and reseating cycles. Moreover, the similar spectra of the worn surfaces with the control indicate that the remaining solid material was not subjected to other structural changes, except for some strong contributions of absorbed water. This water fraction should be strongly bound in the superficial material region, since it was not removed by conventional air-drying, and may increase the hydrolytic susceptibility of the materials. The degree of C=C conversion is a fundamental property for the methacrylate-based dental polymers, as it is related to many mechanical, chemical and biological properties of these materials[221]. The DC% values recorded did not show statistically significant differences between the control and the aligner removal/reseating groups per material or between the materials for the same conditions. The conversion ranged between 61.5-69.7%, which is above the limits for composite restorative materials offering an acceptable abrasive wear depth (~55%)[222].

The results of the present in-vitro study showed that a flowable material was more affected by aligner removal and replacement that a sculptable composite analogue, even in one-week testing period in water. The main issues raised were the higher failure ratio of flowable attachments and the more severe surface deterioration in specimens demonstrating major surface defects. Although the study was performed on zirconia arches, to allow further evaluation of the composite materials eluents, the comparative laboratory conditions employed may establish the need for further studies to elucidate the effects of attachment-aligner interfacial interactions. The loss in attachment-aligner conformity, which may affect the biomechanics of the treatment, the attachment surface roughness in relation to plaque retention capacity, the chemical stability of the worn surfaces and the polymer degradation adducts released are some topics seeking further research to establish the efficiency and safety of the treatment outcome.

In summary, the studies included in the present thesis indicate that aligner thickness does not significantly impact the initial moment-to-force ration exerted on teeth. While aligners effectively address cases involving horizontal tooth movements, their accuracy is inconsistent for incisor intrusions, rotations and torque control. These findings are in accordance with the observation that treatment with aligners tends to yield less favourable treatment outcomes in comparison to fixed appliances, highlighting the potential benefit of over-corrections during treatment planning to minimize the need for refinements. Moreover, caution is advised when recommending aligner cleansing products, since their composition may influence aligner structure resulting in inferior clinical performance. Lastly, the characteristic defects created on the attachments after removal and reseating, highlight the critical role of friction between the aligner and the composite attachment. The release of biological active compounds from attachment surfaces due to this unfavourable outcome has yet to be studied.

7 CONCLUSION

- Although aligner foils generally range between 0.5 and 1mm thickness, the final thickness of the product does not seem to significantly influence the initial forces and moments generated by different types of PET-G thermoplastic aligners, when considering the moment-to-force ratio. The most extensively studied tooth movements include tipping and rotation, with the latter often involving higher rotational forces under specific laboratory conditions. To enhance the robustness of the existing evidence, there is a clear need in establishing standardized protocols, specific types of movement and even aligner design considerations. This would ultimately lead to more conclusive outcomes in the field.
- When comparing predicted and achieved models, no statistically significant differences were observed regarding horizontal tooth movements. Nonetheless, there were significant disparities between predicted and achieved rotations and vertical movements. Particularly, the accuracy of canine rotations and incisor intrusions was notably inconsistent, implying that over-correcting these movements could potentially minimize the necessity for refinement. Given the heterogeneous nature of the malocclusions examined and the limited sample size subsequent research is essential to validate the findings.
- Orthodontic treatment utilizing aligners tends to result in less favourable treatment outcomes in comparison to fixed appliances based on currently available clinical evidence derived from randomized trials and matched non-randomized studies, primarily involving adult patients with mild to severe malocclusions. It is important to note that the duration of treatment does not appear to be solely dictated by the choice of appliance. Instead, various patient and treatment-related factors may play a role. In the context of adverse outcomes such as external apical root resorption (EARR), lower incisor proclination, and the development of gingival recessions, limited data exists. To achieve more robust conclusions, further well-executed individual trials will be essential.
- The mechanical characteristics of the PU aligners (Invisalign, Align Technology) remained unaltered following exposure to various cleaning solutions (two alkaline peroxides and one acidic). Conversely, PET-G aligners (Clear Aligner, Scheu-Dental GmbH) exhibited softening and increased brittleness after immersion in all solutions, along with enhanced relaxation in two solutions (alkaline peroxide and acidic). These changes might be influenced by residual stresses. The surface chemical analysis unveiled the formation of

acids in PET-G aligners after exposure to the acidic treatment. In the case of PU aligners, alterations in surface chemistry were observed only in response to one alkaline cleaner suggesting early indications of degradation. In light of these findings, it is recommended to exercise caution when using the tested cleaners on PET-G aligners, while certain alkaline peroxide solutions should be avoided when cleaning PU aligners.

- Characteristic abrasion-induced defects by removal and reseating of the aligners were detected without significant changes in the roughness parameters (control-tested), but with significant higher values in Sdr between materials within control or tested groups. The sculptable material appeared superior in terms of morphology and retention characteristics. Insignificant differences in the C=C conversion were found in the groups tested. However, in some specimens strong peaks or irreversibly absorbed water were detected indicating hydrolytic susceptibility of the superficial composite zone.

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PUBLICATION
I

Forces and moments generated by aligner-type appliances for orthodontic tooth movement: A systematic review and meta-analysis.

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REVIEW ARTICLE

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Forces and moments generated by aligner-type appliances for orthodontic tooth movement: A systematic review and meta-analysis

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Abstract

The aim of this review was to systematically appraise the evidence on aligner mechanics and forces and moments generated across difference types of aligners. In vitro-laboratory studies for model simulated tooth movement with aligners. Database searches within Medline via Pubmed, Cochrane Central Register of Controlled Trials (CENTRAL), LILACS via BIREME Virtual Health Library. Unpublished literature was also searched in Open Grey, ClinicalTrials.gov (www.clinicaltrials.gov), the National Research Register (www.controlled-trials.com) and Center for Open Science (Open Science Framework), using the terms “aligner” AND “orthodontic”. Risk of bias assessment was based on the Cochrane Risk of Bias tool. Random effects meta-analyses were conducted. A total of 447 studies were identified through electronic search and after careful consideration of pre- defined eligibility criteria, 13 deemed eligible for inclusion, while 2 were included in the quantitative synthesis. When palatal tipping of the upper central incisor through PET-G aligners was considered, aligner thickness of 0.5, 0.625 or 0.75 mm was not associated with a significantly different moment to force (M/F) ratio, given a common gingival edge width of 3-4 mm. Aligner thickness does not appear to possess a significant role in forces and moments generated by clear aligners under specific settings, while the most commonly examined tooth movements are tipping and rotation. The findings of this review may be applicable to certain conditions in laboratory settings.

KEYWORDS
aligner, force, meta-analysis, moment, systematic review, tooth movement

1 | INTRODUCTION

The concept of fabricating aligners on setup casts for orthodontic tooth movement dates back to 1945.[1] Nowadays, the increasing demand for invisible orthodontics and aesthetic considerations, primarily across adult patients, has made the use of thermoplastic aligners quite popular. By the end of the 1990s, two novel thermoplastic aligner systems were introduced allowing for a wide range of tooth movement. The first implemented setups comprising tooth displacements between 0.5 and 1 mm.[2] This required a sequence of three aligners per setup step, with increasing thickness. The second allowed for setup steps to be reduced to ~0.2 mm, so that stiffer aligners could be employed.[3] Stereolithographic models and digital setups were implemented, allowing for only one initial impression.

Notwithstanding, forces and moments generated by such aligner-type appliances on teeth remain largely unknown to clinicians. A number of studies compared the force-delivery properties of thermoplastic orthodontic aligners in terms of setup magnitude. It has been stated that setup increments should preferably range between 0.2 and 0.5 mm, depending on the type of thermoplastic material used.[4] Other studies investigated the forces and moments applied on teeth by thermoplastic aligners in a series of movements. During mesiodistal rotation, forces were exceeding the suggested load of 20 Nmm.[5] Similar findings were confirmed for intrusion, tipping and bodily movement.[6-8]

Clinical behaviour of thermoplastic aligner-type appliances is not unaffected by occlusal forces and/or wear-related properties. The former has been associated with load increases when it comes to rotational moments or intrusive forces.[9] The latter may lead to a considerable force decay and deactivation, which may reach ~50% after a 2-week period of aligner use.[10]

The importance of setup increments in conjunction with the selection of the appropriate thermoplastic foil thickness during aligner manufacturing is pivotal to avoid overloading of teeth during orthodontic movement. Although a number of studies have attempted to quantify the effect of setup increments and thermoplastic material thickness on aligner mechanics, a systematic review and synthesis of the available evidence are lacking from the existing literature. Therefore, the aim of the present review was to systematically search the relevant literature in order to synthesize the available evidence on aligner mechanics and tooth loading for all types of orthodontic tooth movement with aligner-type appliances.

2 | MATERIALS AND METHODS

2.1 | Protocol and registration

A study protocol was specified in advance and registered at PROSPERO (International Prospective Register of Systematic Reviews) no. CRD42019116900.

2.2 | Eligibility criteria

2.2.1 | Study design

In vitro/laboratory studies, studies related to the forces/moments exerted by aligners, any clinical trial/retrospective cohort study with at least two groups for comparison.

2.2.2 | Participants/Population

Models for simulated tooth movement with aligners were considered for in-vitro studies. Participants undergoing orthodontic treatment with aligners (irrespective of age), if applicable, would also be considered.

2.2.3 | Intervention

All types of aligners used for orthodontic tooth movement were considered eligible, irrespective of material type, thickness and activation.

2.2.4 | Comparator

Any type of comparator will be considered, either non-aligner orthodontic devices or different types of aligners (in terms of design, thickness, inclusion of attachments).

2.2.5 | Outcome

Forces and/or moments generated, complying with any type of tooth movement produced (ie rotation, intrusion, torque).

2.2.6 | Exclusion criteria

Diagnostic accuracy studies comparing predicted and final tooth movement, before-after studies, finite element studies.

2.3 | Search strategy and study selection

Detailed electronic search strategies with no language restrictions were developed within seven databases, as of 11 November 2018: Medline via PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), LILACS via BIREME Virtual Health Library. Moreover, unpublished literature was searched in Open Grey, ClinicalTrials.gov (www.clinicaltrials.gov), the National Research Register (www.controlled-trials.com) and Center for Open Science (Open Science Framework), using the terms "aligner" AND "orthodontic". Hand searching of the reference lists of the included studies for full text evaluation was also conducted. Contact with authors of the original studies was implemented to clarify data when needed.

Eligibility assessment was performed independently and in duplicate by two reviewers (AI, DK) not blinded to the identity of the authors of the original studies, their institutions or the results of their research. Titles and abstracts were examined first, followed by full-text evaluation of the potentially included studies. Disagreements were resolved through consultation with a third author (TE), until a consensus was reached. Full search strategy in MEDLINE via PubMed is presented in Appendix 1.

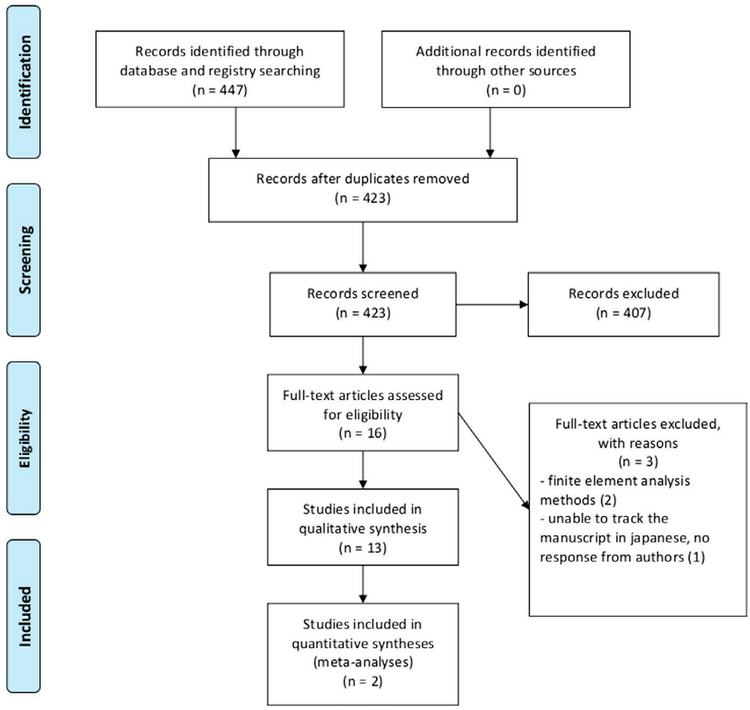
2.4 | Data collection

Data extraction was performed by one reviewer (AI) in pre-piloted forms. The reviewer who was not blinded to author identity or study origin and all information obtained was confirmed by a second (DK). Data derived comprised on details on study design, sample size, interventions/ comparators, tooth type and orthodontic movement examined, outcomes (ie forces, moments).

2.5 | Risk of bias in individual studies

The assessment of the risk of bias was implemented by one author (AI) after calibration with a second (DK) on 15% of the included studies. Entries were confirmed by a second author (DK),

FIGURE 1 Flow diagram of article retrieval



and any disagreements were resolved through discussion with a third author (TE). The risk of bias within the included trials was assessed using the Cochrane risk of bias tool in accordance with the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0[11] (a modification of the tool was used to assess risk of bias in in vitro studies).

2.6 | Summary measures and data synthesis

Clinical heterogeneity of the retrieved and eligible for inclusion studies was assessed through the examination of study settings, eligibility criteria, interventions, experimental conditions prior to intervention assignment, laboratory settings and data collection methods. Statistical heterogeneity was first examined through visual inspection of the confidence intervals (CIs) for the treatment effects on forest plots. A chi-square test was also applied to assess heterogeneity; a *P*-value below the level of 10% ($P < 0.1$) was considered indicative of significant heterogeneity.[12] I^2 test for homogeneity was undertaken as well. Only studies with unclear or low risk of bias overall were intended to be included in the quantitative syntheses. Random effects meta-analyses were conducted as they were considered more appropriate to evince the expected heterogeneity and variations in laboratory settings or simulation conditions. Treatment effects were calculated through pooled standardized mean differences (SMDs) with associated 95% Confidence Intervals (95% CIs) and Prediction Intervals where possible (at least three studies).

2.7 | Risk of bias across studies

If more than 10 studies were included in meta-analyses, publication bias was to be explored through standard funnel plots.

2.8 | Additional analyses

Sensitivity analyses were predetermined to explore and isolate the effect of studies with unclear risk of bias on the pooled treatment effect if both low and unclear risk of bias studies were included.

3 | RESULTS

3.1 | Search details

A total number of 447 studies were retrieved and the aforementioned inclusion criteria were applied. The flow chart describing the study identification process is presented in Figure 1. After abstract- and full-text reading stage, 13 studies were considered eligible for this review (Table 1). All 13 studies were in vitro studies.

3.2 | Study design and characteristics

All included studies were published between 2010 and 2018 and reviewed 6 different aligner materials (Biolon, Erkodur, Ideal Clear, Duran, All-In, Invisalign) with foil thickness from 0.3 to 1 mm. Six

TABLE 1 Characteristics of the included studies (n = 13)

id	Author and Year of Publication	Study design	Sample size/teeth type	Groups under comparison	Interventions	Outcomes
1	Brockmeyer et al (2017)	in vitro	Total n = 45 aligners, same thickness 1mm Biolon uncut n = 5, z11 n = 5, z12-21 n = 5 Erkodur uncut n = 5, z11 n = 5, z12-21 n = 5 IdealClear uncut n = 5, z11 n = 5, z12-21 n = 5 upper central incisor	Material vs cut, deflection distance vs material, deflection distance vs cut	Thermoplastic aligners modified by incisal cuts	Horizontal force component magnitude, vertical force component magnitude in labial and palatal translation of upper central incisors
2	Elkholy et al (2015)	in vitro	Total n = 27 aligners Duran 0.5 mm (n = 3), 0.625 mm (n = 3), 0.75 mm (n = 3) Erkodur 0.5 mm (n = 3), 0.6 mm (n = 3), 0.8 mm (n = 3) Track-A 0.5 mm (n = 3), 0.63 mm (n = 3), 0.8 mm (n = 3) upper central incisors	Forces delivered aligner/ thickness	Different aligner thickness n material Duran 0.5 mm (n = 3), 0.625 mm (n = 3), 0.75 mm (n = 3) Erkodur 0.5 mm (n = 3), 0.6 mm (n = 3), 0.8 mm (n = 3) Track-A 0.5 mm (n = 3), 0.63 mm (n = 3), 0.8 mm (n = 3)	Forced and moments magnitude to upper central incisor for labial and palatal translation
3	Elkholy et al (2016)	in vitro	Total n = 15 Duran 0.3 mm (n = 3) 0.4 mm (n = 3) 0.5 mm (n = 3) 0.625 mm (n = 3) 0.75 (n = 3) upper central incisors	Forces delivered aligner/ thickness	Reduced thickness aligners Duran 0.3 mm (n = 3) 0.4 mm (n = 3) 0.5 mm (n = 3) 0.625 mm (n = 3) 0.75 (n = 3)	Forces and moments delivered during labiopalatal movement of upper central incisor
4	Elkholy et al (2017) (AJODO)	in vitro	Total n = 15 Duran 0.5 mm (n = 3), 0.625 mm (n = 3), 0.75 mm (n = 3) vs 0.3 mm (n = 3), 0.4 mm (n = 3) upper central incisors	Forces applied by 0.3/0.4 mm aligners vs conventional >0.5 mm	Reduced thickness aligners 0.4, 0.3 mm Duran 0.5 mm (n = 3), 0.625 mm (n = 3), 0.75 mm (n = 3) vs 0.3 mm (n = 3), 0.4 mm (n = 3)	Forces and moments delivered during mesiodistal derotation of upper central incisor
5	Elkholy et al (2017) (J Orofac Orthop)	in vitro	Total n = 9 Duran 0.5 mm (n = 3), 0.625 mm (n = 3), 0.75 mm (n = 3) mandibular canine	Forces delivered aligner/ thickness	Duran 0.5 mm (n = 3), 0.625 mm (n = 3), 0.75 mm (n = 3)	Forces and moments delivered during mesial and distal derotation of mandibular canine
6	Gao et al (2017)	in vitro	Total n = 27*2 = 54? Duran 0.5 mm/0-1 width n = 3 Duran 0.5 mm/3-4 width n = 3 Duran 0.5 mm/6-7 width n = 3 Duran 0.625 mm/0-1 width n = 3 Duran 0.625 mm/3-4 width n = 3 Duran 0.625 mm/6-7 width n = 3 Duran 0.75 mm/0-1 width n = 3 Duran 0.75 mm/3-4 width n = 3 Duran 0.75 mm/6-7 width n = 3 Upper central incisor	Edge width comparison/ aligner thickness	Different aligner thickness width Duran 0.5 mm/0-1 width n = 3 Duran 0.5 mm/3-4 width n = 3 Duran 0.5 mm/6-7 width n = 3 Duran 0.625 mm/0-1 width n = 3 Duran 0.625 mm/3-4 width n = 3 Duran 0.625 mm/6-7 width n = 3 Duran 0.75 mm/0-1 width n = 3 Duran 0.75 mm/3-4 width n = 3 Duran 0.75 mm/6-7 width n = 3	Forces and moments delivered during maxillary central incisor palatal tipping and intrusion

(Continues)

TABLE 1 (Continued)

id	Author and Year of Publication	Study design	Sample size/teeth type	Groups under comparison	Interventions	Outcomes
7	Hahn et al (2010) (Angle)	in vitro	n = 15 Ideal Clear 1 mm n = 5 Erkodur 1 mm n = 5 Biolon 1 mm n = 5 Upper central incisor	Forces delivered aligner material	Different aligner material	Force system and moments produced by 3 different types of plastic aligners during rotation
8	Hahn et al (2010) (EJO)	in vitro	n = 15 Ideal Clear 1 mm n = 5 Erkodur 1 mm n = 5 Biolon 1 mm n = 5 Upper central	Forces delivered aligner material	Different aligner material	Force system and moments produced by 3 different types of plastic aligners during torque
9	Hahn et al (2011)	in vitro	n = 20 Biolon 0.75 mm n = 5 Biolon 1 mm n = 5 Erkodur 0.8 mm n = 5 Erkodur 1 mm n = 5 upper central	Forces delivered material/with and without simulated occlusal forces	Different aligner material + occlusal forces	Forces produced by two different types of aligners with and without simulated occlusal forces during rotation of upper central incisors
10	Li et al (2016)	in vitro	n = 5, Erkodur 1 mm activation 0.2 mm n = 1 activation 0.3 mm n = 1 activation 0.4 mm n = 1 activation 0.5 mm n = 1 activation 0.6 mm n = 1 upper central	Forces delivered between various amounts of activation aligners	Aligners with various amounts of activation	Forces delivered between various amounts of activation aligners and attenuation during lingual bodily movement of upper central incisor
11	Liu et al (2018)	in vitro	n = 55, Duran 0.8 mm thickness G0 control n = 5 G1 intrude mand canines by 0.2 mm n = 5 G2 intrude 4 mand incisors by 0.2 mm n = 5 G3 intrude canines and inc by 0.2 mm n = 5 G4 intrude can 0.1 mm, lat inc 0.15 mm, centr inc 0.2 mm plus attachments on 1st and 2nd premolars and 1st molars	G0, G1, G2, G3, G4	Aligners with different activation	Forces delivered between various types/amount of aligner activation during intrusion of lower anterior
12	Mencattelli et al (2015)	in vitro	All in, Micerium n = 3 -aligner with no forces n = 1 -aligner without divot n = 1 -aligner with divot n = 1 maxillary central incisor	With divot/without divot	Aligner with divot	Forces delivered from aligner with divot during rotation

(Continues)

TABLE 1 (Continued)

id	Author and Year of Publication	Study design	Sample size/teeth type	Groups under comparison	Interventions	Outcomes
13	Simon (2014)	in vitro	n = 970 aligners (60 series/30 patients) Invisalign incisor torque*, n = 10 patients (split mouth torque <10o + attachment) premolar derotation*, n = 10 patients (split mouth derotation <10o + attachment) molar distalization*, n = 10 patients (split mouth distalization <1.5 mm + attachment)*20 tooth movements (2 per patient)	With/without attachments in specific movements: torque, derotation, distalization	With/without attachments	Initial force systems that are delivered by an individual aligner, force systems generated by a series of aligners, influence of auxiliaries (attachments, power ridges) on the force transfer

distinctive types of tooth movement were described with the use of the aforementioned aligner combination thickness (Table 1).

3.3 | Risk of bias within studies

The risk of bias of the thirteen included in vitro studies was assessed using a modified version of the Cochrane risk of bias tool[11] (Figure 2). Eleven studies[6-9,13-19] stated clearly the experimental conditions which were comparable between groups. Blinding of the assessors was considered unclear. Losses or non-inclusion of specimens were not reported thus no attrition bias was detected and there was no evidence of selective outcome reporting. Based on the aforementioned points these studies were classified as unclear risk of bias.

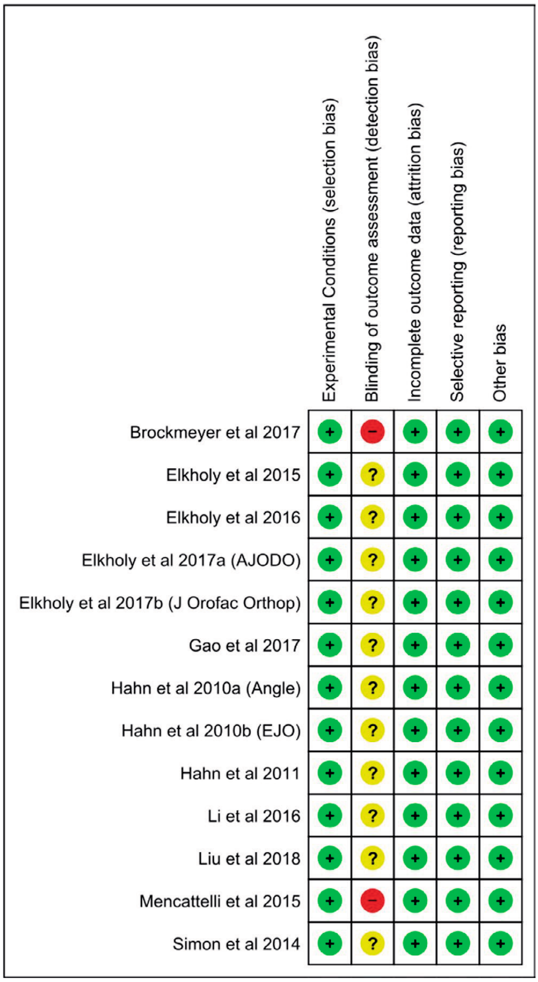


FIGURE 2 Risk of bias summary outlining judgement of risk of bias items for each of the included studies. The plus sign indicates low risk of bias; the circle with question mark indicates unclear risk of bias; the minus sign indicates high risk of bias

In two studies,[20,21] blinding of the assessors was not feasible due to the nature of the interventions thus, these studies were rated as high risk of bias.

3.4 | Effects of interventions, meta-analyses and additional analyses

3.4.1 | Effects of interventions

Quantitative synthesis of included studies

Quantitative analysis was only feasible between two of the included studies,[6,8] and pertained to palatal tipping movement of maxillary central incisor, generated by PET-G aligners trimmed to a gingival edge width of 3-4 mm. There was no difference between any of the retrieved aligner thickness comparisons with regard to moment to force (M/F) ratio. More specifically, for aligner thickness of 0.5 mm compared to that of 0.75 mm the pooled estimate was a standardized mean difference (SMD) of −3.33 (95% CI: −9.63, 2.96; *P*-value = 0.30; I^2 = 82.0%; Figure 3). Accordingly, no differences to M/F ratio were detected for comparisons between 0.5 and 0.625 mm thickness (SMD = −0.43; 95% CI: −4.16, 3.29; *P*-value = 0.82; I^2 = 84.1%; Figure 4), or 0.625 to 0.75 mm (SMD = −0.98; 95% CI: −7.41, 5.46; *P*-value = 0.77; I^2 = 89.9%; Figure 5), as well.

Qualitative synthesis of included studies

The included studies were examined from three different perspectives regarding aligner thickness, generated tooth movement and aligner material. This arbitrary categorization was implemented simply to facilitate data comprehension.

3.4.2 | Aligner thickness

The thickness of plastic foil used for thermoforming PET-G aligners ranged from 0.3 to 1 mm. The forces generated by the thinnest commercially available aligners of 0.5 mm resulted in significant overloading of the periodontal structures.[7] When PET-G aligners of reduced thickness, namely of 0.4 and 0.3 mm were used, the aforementioned forces were decreased by 35% and 71%, respectively.[7] It has been reported that aligner thickness of 0.3 mm, may reduce rotational stiffness by 76%.[14] Despite the fact that 0.3 mm PET-G aligners seem to exert ideal forces, they are considered unsuitable for clinical use due to deformation.[7,14] Thus, a sequence of aligners including 0.4, 0.5, 0.75 mm has been proposed[7,14,15] in order to achieve low initial stiffness combined with a steady load. As for 0.625 and 0.75 mm PET-G foils, findings indicate that both presented similar mechanical behaviour with respect to rotational moments during mandibular canine and maxillary central incisor rotation[14,15] as well as labio-lingual tipping and bodily movement.[6-8] Three studies[9,13,16] examined the behaviour of 1 mm PET-G aligners and concluded that forces and moments generated were higher than those recommended. Finally, forces applied by 0.7 mm Invisalign system aligners have been reported to lie within the range of acceptable orthodontic forces.[19]

3.4.3 | Type of tooth movement

Tipping of upper central incisors[20] and lower canine intrusion[18] is feasible with the use of PET-G aligners. On the contrary, three studies[7,16,17] indicated that bodily movement and torque are the most demanding movements to achieve since plain aligners without modifications cannot establish the force couple required. Upper incisor rotation movement with aligners has been frequently coupled with an intrusive force, which may present an increase in magnitude when combined with simulated occlusal forces.[9,13,14] Hahn et al,[13] found that only a slight activation of ±0.17 mm or 0.5° per step during rotation could produce ideal forces which have been estimated to range between 0.35 and 0.6 N.[22] Finally, Simon et al stated that Invisalign aligners bear the potential to deliver force levels of such magnitude, which may produce premolar derotation, bodily movement, molar distalization and torque when combined with appropriate attachment setups.[19]

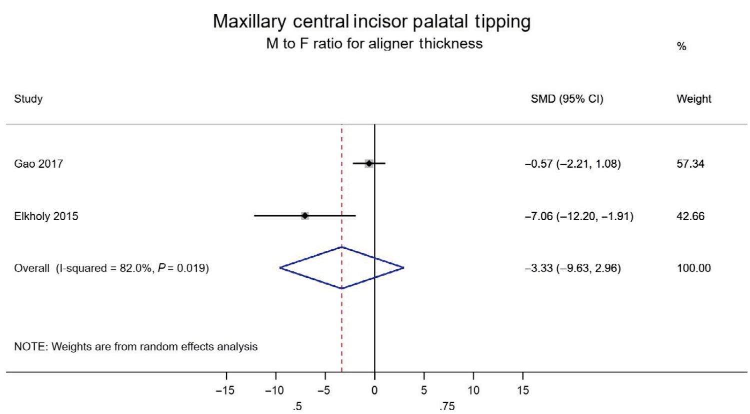


FIGURE 3 Random effects meta-analysis for the effect of aligner thickness on moment to force (M/F) ratio, for palatal tipping of the upper central incisor (aligner thickness: 0.5 mm vs 0.75 mm)

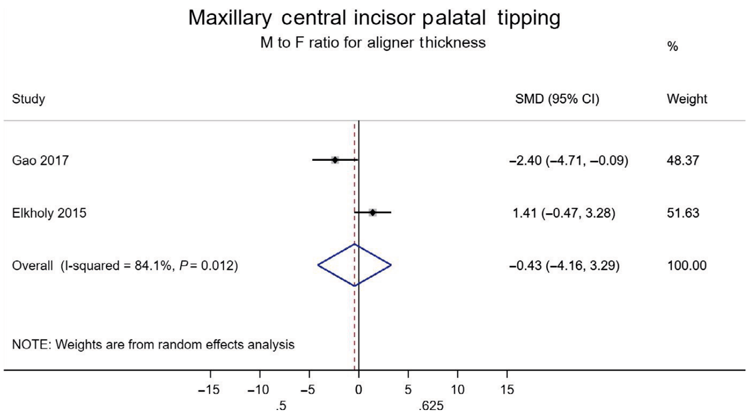


FIGURE 4 Random effects meta-analysis for the effect of aligner thickness on moment to force (M/F) ratio, for palatal tipping of the upper central incisor (aligner thickness: 0.5 mm vs 0.625 mm)

3.4.4 | Aligner material

All four studies[9,13,16,20] comparing different PET-G aligner materials of 1 mm thickness reported that aligners vacuum-formed with Biolon (Dreve Dentamid GmbH, Unna, Germany) delivered the highest forces and moments ranging from 1.15 to 6.19 N[16,20] during tipping and 35.3-71.8 Nmm[9,13] during rotation, depending on the activation magnitude. The only exception was observed during rotation at low rotation range of ±0.17 mm were the Ideal Clear appliance (Dentsply GAC, Gräfelfing, Germany) exerted the highest values (18.3-20.2 Nmm).[13] Finally, the lowest forces and rotational moments were reported for Erkodur (Erkodent Erich Kopp GmbH, Pfalzgrafenweiler, Germany) at all activation ranges.[9,13,16,20]

Finally, three studies[19-21] reported the importance of aligner modifications in order to achieve the desired rotation. The use of divots corresponding to the tooth to be treated was found to increase rotational forces by 58%,[21] whereas the placement of attachments in teeth with short crowns and few undercuts facilitated as well the delivery of the necessary force system.[20]

3.5 | Risk of bias across studies

Exploring for publication bias either statistically or graphically was not possible as no more than 3 studies contributed to individual quantitative syntheses.

4 | DISCUSSION

To the best of our knowledge, this is the first attempt to systematically appraise the evidence on forces and moments generated by aligner-type adjuncts related to orthodontic tooth movement. It was clear that only laboratory studies were identified and subsequently included as the sole source of evidence. Overall, between study heterogeneity and apparent differences in settings, aligner material and type, tooth type and type of movement precluded concrete comparisons between aligner types.

Based on qualitative synthesis, it was evident that one of the thinnest commercially available aligners of 0.5 mm (PET-G aligners) resulted in a non-negligible overloading of teeth which might apparently impact on periodontal structures.[7] Nevertheless, this is compliant with the desired tooth movement. In order to achieve low initial stiffness, a sequence of aligners including an initial aligner of 0.4 mm thickness has been proposed,[7,14,15] while Invisalign (Align Technology) utilizes an adjunct of 0.7 mm. Furthermore, the required force couple to achieve bodily movement and torque cannot be established with the use of plain aligners. Thus, modifications such as attachments, divots and cuts are proposed in order to facilitate the desired tooth movement.[19-21] Aligners vacuum formed with Biolon delivered the highest moments and forces when compared to Erkodur, although the results were statistically significant only in specific settings.

Friction phenomena, deformations created at the contact areas during thermoforming as well as polymer material may explain the differences on mechanical behaviour between Biolon and Erkodur.[13,20] The former appliances are thermoformed with a pressure of 6 bars, whereas the latter are vacuum- formed with 0.8 bars.[20] Moreover, according to the manufacturer's instructions a spacing foil of 0.05 mm thickness placed between tooth and appliance should be used during thermoforming of Erkodur appliances.[13,20] Although this foil would experience a certain amount of shrinkage after thermoforming, one can assume that its final thickness could be comparable to one activation step.

The quantitative synthesis did not reveal a clear difference between the thinnest commercially available aligners of 0.5 mm and its counterpart of either 0.625 or 0.75 mm in terms of moment to force ratio. Material of increased thickness may reach higher levels of rigidity; however, this does not result in higher levels of effectively exerted forces that may translate to clinical implications. It has been suggested that the intermediate stage

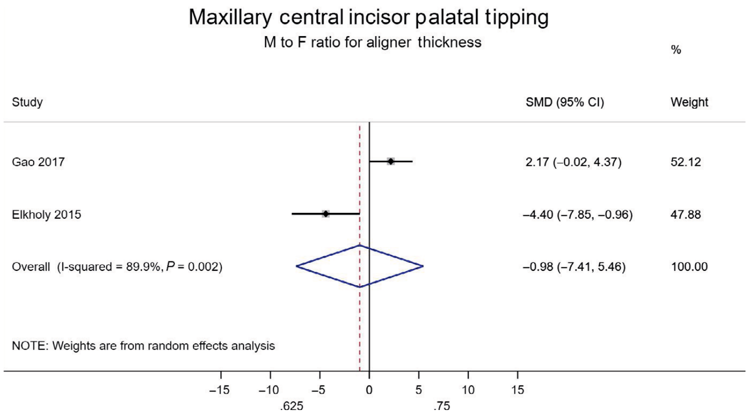


FIGURE 5 Random effects meta-analysis for the effect of aligner thickness on moment to force (M/F) ratio, for palatal tipping of the upper central incisor (aligner thickness: 0.625 mm vs 0.75 mm)

thickness of these adjuncts such as 0.625 may be questionable or even unnecessary in the clinical context.[8] This is in contrast with the existing recommendations for clinical use of three consecutive aligners of increasing thickness very close to one another.[23] In essence, in the study of Elkholy et al,[6] the authors' intention was to identify possible evidence of translational palatal movement of the central incisor; however, this was not achieved as the final exerted forces showed negligible amounts of bodily movement and was ultimately a result of tipping increments. Moreover, the detected findings were based on aligners with a gingival edge width of 3-4 mm.

Reporting of the included studies was positive overall and allowed for a comprehensive assessment of risk of bias within studies. In general, efforts should be directed in optimizing laboratory conditions that would allow researchers remain blinded when feasible during the assessment of the efficiency of different types of aligners in terms of biomechanical considerations. Moreover, it should be noted that although the risk of selective outcome reporting was minimum given the adequate matching of the reported variables within the methodology section and the results, no study was registered a priori or described a published protocol.

In- vitro studies in laboratory conditions may effectively represent initial tooth movement mechanics. As such, the reported levels of forces or moments are the highest that may have been generated overall. Force decay produced by thermoplastic aligners over a two-week period has been documented between 50% of the initial magnitude[10] and a 5-fold decrease.[23] Tooth movement is described by an interaction of forces and moments exerted and as such, the metric 'moment to force ratio' is the one that better represents the simulated tooth movement conditions, for tipping and translational movements, irrespective of the anticipated magnitude of the movement. However, gingival edge width of the aligner has been identified as a significant predictor of at least the initial moments/forces generated by the aligners. Intrusive movements have been reported to be particularly prone to edge width configuration than tipping movements, while edgeless aligners have been associated with decreased force levels.[8]

The present review was prospectively registered with an a priori protocol specification and followed a clear and transparent methodology on reported parameters and outcomes. A full search strategy was employed within seven databases, comprising both published and unpublished literature, in an attempt to minimize publication bias. Nevertheless, the review is subject to certain limitations. First, only two studies contributed to quantitative syntheses, over a very specific type of tooth movement on the upper central maxillary incisor and under the spectrum of high degree of heterogeneity. Thus, the findings may only be generalizable to a very limited range of material-tooth interface interactions. Second, data acquired are based on laboratory simulation conditions and cannot be directly transferred to biologic mechanisms of tooth movement within the periodontal ligament. In addition, tooth movement biomechanics have been studied across included studies on a single-tooth specific frame, without consideration of adjacent teeth, elastic modulus of the ligament, occlusal/ mastication forces or soft tissue considerations. Finally, in- vitro studies may suffer from inherent bias due to the lack of standardization of procedures followed to determine the desired effects. In general, specific measuring devices connected to mounted tooth models via a group of sensors and complying to a coordinate system allowing for tooth mobility and simulation of the periodontal ligament have been used. Apparently, any variation within the described laboratory set- up across individual studies may result in heterogeneous results. As such and following guidelines from clinical research, there is an overriding need for the development of consistent study protocols prior to study commencement, as well as for the agreement on the experimental settings and the most valuable core outcome sets to be universally used.[24]

5 | CONCLUSIONS

Use of fabrication material of the aligners was confined to different types of PET-G. Aligner thickness does not appear to play a significant role over initial forces and moments generated by thermoplastic aligners in terms of moment to force ratio. Foils have been typically reported to range between 0.5 and 1 mm. The most widely examined tooth movements are tipping and rotation, with rotational forces ascending to a much higher level. However, the findings of this review may be applicable to specific conditions and tooth movements in laboratory settings. Overall, there is a need for standardized protocols, types of movements or design of the aligners in order to inform the existing evidence with more conclusive outcomes.

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None.

CONFLICT OF INTEREST

None.

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APPENDIX 1

MEDLINE search

Date: November 9, 2018

Limits: no language restriction applied

Publication date: no restriction

Search Builder: 'All Fields'

Two consecutive searches combined with 'AND' Boolean operator, using 'OR' between free text terms or keywords:

1. invisalign
2. aligner
3. aligners
4. aligner*
5. thermoplastic aligner
6. thermoplastic aligner*
7. 1 OR 2 OR 3 OR 4 OR 5 OR 6
8. force
9. forces
10. force*
11. orthodontic movement
12. orthodontic movements
13. orthod* movements
14. orthodontic force
15. orthodontic force*
16. orthodontic moments
17. orthodontic moment
18. moment
19. moments
20. torque
21. torque control
22. 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21
23. 7 AND 22

PUBLICATION
II

Accuracy of clear aligners: A retrospective study of patients who needed refinement.

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Accuracy of clear aligners: A retrospective study of patients who needed refinement

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St Louis, Mo, and Athens, Greece

Introduction: The purpose of this study was to determine the accuracy of specific tooth movements with Invisalign (Align Technology, Santa Clara, Calif). **Methods:** The study sample included 20 Class I adult patients treated with Invisalign; they completed their first series of aligners and had to have a "refinement" series. Initial and predicted models were obtained from the initial ClinCheck (Align Technology). The starting point of the refinement ClinCheck was used to create the achieved models. Predicted and achieved models were superimposed over the initial ones on posterior teeth using the 3-dimensional Image Analysis open-source software Slicer CMF. Three hundred ninety-eight teeth were measured for vertical, horizontal, and rotational movements, and transverse widths were measured. The amount of predicted tooth movement was compared with the achieved amount for each movement. **Results:** Horizontal movements of all incisors seemed to be accurate, with small (0.20-0.25 mm) or insignificant differences between predicted and achieved amounts. Vertical movements and particularly intrusions of maxillary central incisors were found to be less accurate, with a median difference of 1.5 mm ($P < 0.001$). All achieved rotations were significantly smaller than those predicted, with the maxillary canines exhibiting the greatest difference of 3.05° ($P < 0.001$). **Conclusions:** The most inaccurate movements identified in this study were intrusion of the incisors and rotation of the canines. (Am J Orthod Dentofacial Orthop 2018;154:47-54)

The Invisalign appliance was introduced to the public in the late 1990s by Align Technology (Santa Clara, Calif) as a novel method of straightening teeth without braces. Since then, Invisalign has made great progress in terms of treatment planning methods, materials, and manufacturing. The company's powerful marketing has helped to increase the public's demand for clear aligners to the point where Invisalign is an essential part of any orthodontic practice today. There is much speculation regarding its future and the future of orthodontics; however, there is no strong evidence regarding the capabilities and limitations of clear aligners.

In recent years, researchers have used several methods including the American Board of Orthodontics objective grading system, Peer Assessment Rating scores, and other objective occlusal criteria to assess the quality of Invisalign treatment.[1-12] The most notable conclusions were that Invisalign is not as effective as fixed appliances for expansion,[6] it seems to cause more relapse,[5] and it is not very effective in controlling buccolingual inclination,[4,10,11] occlusal contacts,[4,10,11] occlusal relationships,[4,11] overjet,[4] and overbite.[7] Although these are relatively simple and objective methods of evaluating treatment outcomes, they have some limitations and do not explain the etiology of unsatisfactory results in depth.

A different way of evaluating the accuracy of Invisalign is 3-dimensional (3D) superimposition of predicted and achieved models. A few studies have used 3D superimpositions to measure the accuracy of different types of tooth movements, but the results have been unclear.[13-17] A major limitation of 3D superimpositions is the lack of stable anatomic structures on the predicted models, since ClinCheck (Align Technology) only contains clinical crowns and virtual gingiva. Well-conducted studies of this kind could provide valuable information for efficient treatment planning with ClinCheck. For example, if the accuracy percentage of a specific tooth movement is known, overcorrecting it by the appropriate amount or staging the movement in smaller increments may result in the desired outcome.

Previous studies have obtained valuable information, but there is still much to be learned about the biomechanics and limitations of clear aligners. According to a recent systematic review, the quality of available

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studies was not sufficient to draw evidence-based conclusions.[18] Much of what we know about Invisalign is still based on clinical experience rather than scientific evidence.[15]

In addition, the studies that used 3D superimpositions were performed before the introduction of the new aligner material called SmartTrack (Align Technology) in 2013. According to Align Technology's anecdotal research, it has superior properties compared with standard Essix materials and can exert continuous forces over a longer period of time. Despite the technological advances and changes that the Invisalign appliance has undergone, clinicians still find that a refinement stage is often necessary.

The aim of this study was to determine the accuracy of specific tooth movements with Invisalign to identify possible reasons for refinement.

MATERIAL AND METHODS

The study group comprised 20 adult patients (3 men, 17 women) with an average age of 37 years 6 months (range, 18 years 1 month to 79 years 11 months). Crowding ranged from mild (0-3 mm) in 7 subjects to moderate (3-6 mm) in 8 subjects and severe (>6 mm) in 3 subjects, and 2 patients had minor spacing. Overbites were deep in 13 subjects, but those with normal overbite (4) and anterior open bite (3) were also included. The study protocol was approved by the Institutional Review Board of Saint Louis University (number 27561). All patients received Invisalign treatment in the Department of Orthodontics at Saint Louis University or a private practice under the supervision of the same orthodontist (●●●), who is an Invisalign elite provider. The orthodontist planned all the ClinChecks according to his preferences with no restrictions on attachment placement. Aligners were changed every 2 weeks. Average treatment time was 12 months (±2.5 months). All patients started treatment in 2014 or later, after Invisalign introduced the SmartTrack material. Inclusion criteria were predefined as follows: (1) all patients received treatment in both arches, (2) all participants successfully completed an initial series of aligners and then had a "refinement" phase, because the treatment goals were not reached, (3) patient charts indicated good compliance with consistent aligner wear, (4) minimal movement of the molars in all 3 planes was planned, and (5) treatment started in 2014 or later. Exclusion criteria were (1) noncompletion of the initial series of aligners, (2) poor compliance, (3) dental restorations before refinement, (4) posterior crossbite, and (5) missing first or second molars.

Twenty-nine potential subjects were identified after searching the university's and the private orthodontist's accounts on the Invisalign doctor Web site. After review of patients' charts, 20 patients met the inclusion and exclusion criteria. Despite minimal planned movement of the molars, superimpositions of the initial and achieved models showed that the intermolar width changed by 0.81 mm (±0.57 mm) on average.

Records were gathered from the Invisalign doctor Web site. Digital models were exported from ClinCheck as stereolithography files. The initial and final models from the first ClinCheck were labelled as "initial" and "predicted." The initial models of the refinement ClinCheck were labelled as "achieved," since they depicted the actual result after aligner wear.[8]

Initial, predicted, and achieved digital models were imported in SlicerCMF (open-source, version 3.1; http://www.slicer.org). The predicted and achieved models were superimposed over the initial ones with regional superimpositions on molars that appeared relatively stable in ClinCheck. The central pits of the first and second molars were traced, and an area of equal radius around them was selected. The regions of interest were limited to the occlusal surfaces if there were attachments (Fig 1), or otherwise the whole crown was selected. Maxillary and mandibular arches were superimposed and measured separately.

Measurements were made on the initial vs predicted and initial vs achieved models to identify the magnitude and direction of the predicted and achieved movements. Predicted and achieved models were not superimposed on each other. The total number of teeth measured was 398. For every subject, 100 measurements were made (50 predicted and 50 achieved movements) for horizontal movements, vertical movements, rotations, and transverse changes as follows.

1. Horizontal displacements (parallel to the occlusal plane) were measured with the ruler tool at the middle of the incisal edges or cusp tips when the models were viewed directly from the occlusal view (Fig 2).
2. Vertical displacements were measured at the middle of the incisal edges or cusp tips (Fig 2).
3. Intercanine and interpremolar widths were measured at the canine cusp tips and the central grooves or central fossae (depending on the anatomic variation) of the second premolars (Fig 3).
4. Mesiodistal rotations were measured by tracing 2 points on the incisal edges of the incisors: the most mesial and most distal points of the canines and the labial and lingual cusp tips of the premolars. The 2 points were connected on each model with a straight line, and then the angle (yaw) between the lines was measured on the horizontal plane (Fig 4).

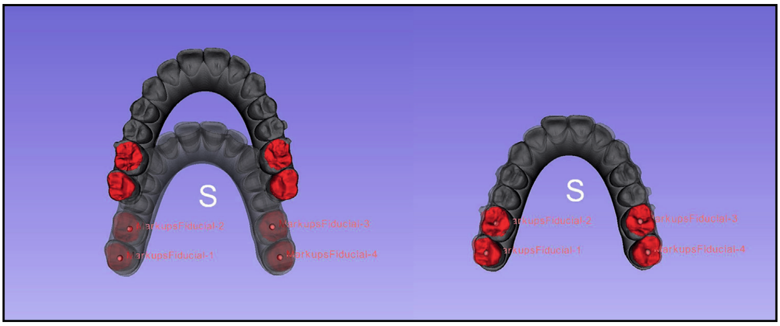

Fig 1. Tracing of central pits and regions of interest (*left*) and superimposed models (*right*).

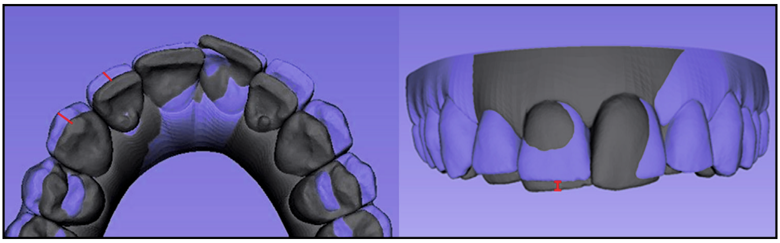

Fig 2. Horizontal and vertical measurements on initial (*grey*) vs predicted (*blue*) superimposed models.

Statistical analysis

The statistical analysis was performed with SPSS software (version 24.0; IBM, Armonk, NY). Each tooth movement was measured separately. Then the teeth were grouped together as follows to reduce the number of variables: contralateral teeth, first and second premolars, and mandibularr central and lateral incisors.

Direction was not considered for horizontal movements and rotations. There was no distinction between labial and lingual displacements as well as clockwise and counterclockwise rotations. However, vertical movement of the incisors was divided into intrusion and extrusion based on the predicted movement. This was considered necessary, since these movements have the opposite effect on overbite, and the literature suggests that one is more predictable than the other.[16]

Descriptive statistics were calculated for each movement. The data distribution was not normal, so the Wilcoxon signed-rank test was used. The level of significance was set at 0.002 after applying the Bonferroni adjustment to control for type I error. The power for the movement with the smallest sample size (n = 18) was 95%.

To assess reliability, 1 month after the initial measurements, 10% of the subjects were remeasured by the same examiner. Intraclass correlation coefficients showed high intraobserver reliability, with Cronbach's alpha ranging from .813 to .994 for linear measurements and .832 to .994 for angular measurements.

RESULTS

Descriptive statistics of the predicted and achieved tooth movements are presented in Table I.

Wilcoxon signed-rank tests between predicted and achieved measurements were performed to assess the accuracy of each movement. The results are given in Table II. A negative value indicates that the achieved values were greater than the predicted ones.

Overall, horizontal movements of all incisors seemed to be accurate, with differences either small (0.20-0.25 mm) or insignificant. Extrusion of incisors also appeared to be accurate, since no statistically significant differences were observed. Conversely, intrusion of incisors was the most inaccurate of all linear movements. The maxillary central incisors had the greatest difference of 1.5 mm (P <0.002).

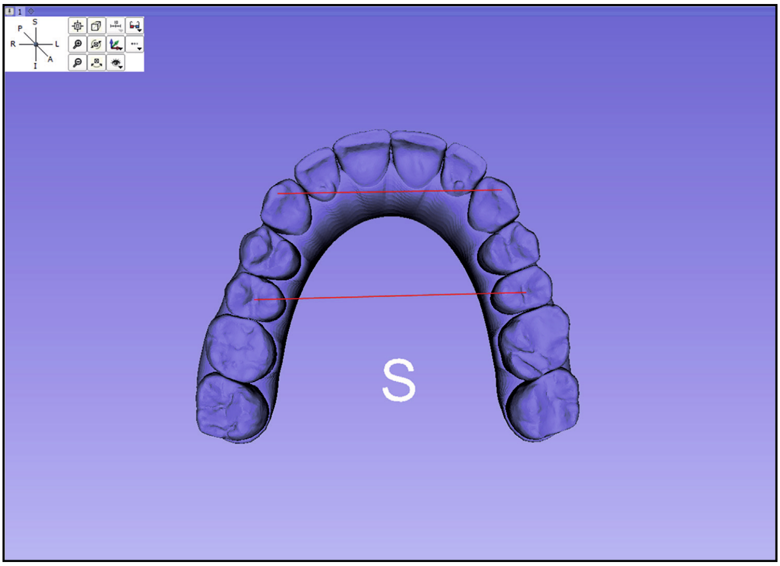

Fig 3. Intercanine and interpremolar widths. The orientation tool on the top left allows for repeatable positioning of the models.

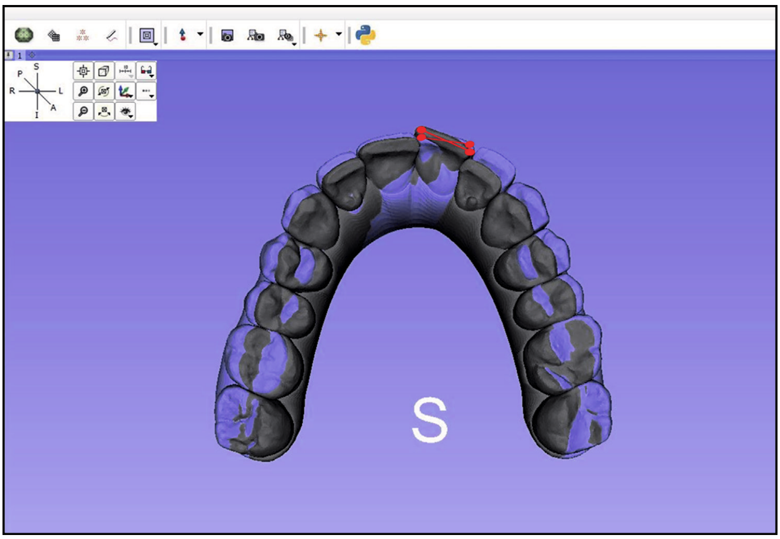

Fig 4. Rotation of a maxillary central incisor.

Table I. Descriptive statistics

Movement	n	Predicted Mean	Predicted Median	Predicted SD	Achieved Mean	Achieved Median	Achieved SD
Maxillary central incisors horizontal (mm)	40	1.14	1.00	0.98	0.90	0.65	0.82
Maxillary lateral incisors horizontal (mm)	40	1.14	0.80	0.88	0.88	0.60	0.77
Maxillary canines horizontal (mm)	40	1.11	1.15	0.76	0.84	0.80	0.65
Maxillary central incisors intrusion (mm)	22	0.99	1.00	0.49	−0.37	−0.25	0.75
Maxillary central incisors extrusion (mm)	18	1.28	1.35	0.79	1.64	1.80	1.02
Maxillary lateral incisors intrusion (mm)	18	0.70	0.50	0.64	−0.22	−0.40	0.76
Maxillary lateral incisors extrusion (mm)	22	0.97	0.90	0.72	1.24	0.95	0.86
Maxillary canines vertical (mm)	40	0.61	0.30	0.71	0.70	0.50	0.71
Maxillary intercanine width change (mm)	20	2.09	2.05	1.20	1.60	1.45	1.06
Maxillary interpremolar width change (mm)	20	1.49	1.45	1.08	1.16	1.10	0.86
Maxillary central incisors rotation (°)	40	5.45	4.40	4.22	3.12	2.15	3.01
Maxillary lateral incisors rotation (°)	40	9.16	6.50	8.04	6.06	3.75	6.56
Maxillary canines rotation (°)	40	8.83	6.50	7.95	5.00	2.50	5.42
Maxillary premolars rotation (°)	79	4.07	3.40	3.59	3.02	2.00	2.89
Mandibular incisors horizontal (mm)	80	1.13	1.00	0.80	1.11	1.00	0.82
Mandibular canines horizontal (mm)	40	1.21	1.00	1.03	1.03	0.80	0.87
Mandibular incisors intrusion (mm)	64	1.33	1.10	0.85	0.34	0.30	0.70
Mandibular incisors extrusion (mm)	16	0.67	0.25	0.86	0.58	0.40	0.44
Mandibular canines vertical (mm)	40	0.86	0.70	0.62	0.44	0.40	0.40
Mandibular first premolars vertical (mm)	40	0.37	0.20	0.42	0.38	0.30	0.30
Mandibular intercanine width change (mm)	20	1.90	1.85	1.21	1.85	1.65	1.16
Mandibular interpremolar width change (mm)	20	1.76	1.25	1.70	1.67	1.50	1.56
Mandibular incisors rotation (°)	80	10.83	7.75	8.99	8.19	5.95	7.37
Mandibular canines rotation (°)	40	13.19	11.40	10.69	9.34	7.95	7.40
Mandibular premolars rotation (°)	79	7.76	5.90	6.42	5.05	3.90	4.54

A negative sign indicates that the opposite movement was observed (extrusion).

The discrepancy for horizontal movement of the canines was significant in the maxilla ($P < 0.001$) but not in the mandible. That was also reflected by the intercanine width change. Vertical canine movement seemed to be more predictable in the maxillary arch than in the mandibular arch, although the planned movement for the mandibular arch was greater.

Interpremolar expansion was accurate for both arches. Vertical movement of the mandibular first premolars did not show a significant discrepancy, but the median planned movement was only 0.2 mm.

For rotations, the findings were statistically significant for all teeth. The canines had the greatest discrepancies of 3.05° in the maxillary arch and 2.45° in the mandbular arch. The maxillary premolars had the lowest discrepancy of only 0.9°.

DISCUSSION

To be able to interpret the results properly, certain limitations of this study should be discussed. The risk of selection bias could not be prevented, due to the retrospective nature of the study. Participants were treated with Invisalign, because a highly experienced practitioner decided that they could be treated effectively with the system. However, since they had refinement at the end implies that treatment was somewhat unsuccessful, so the results should not be generalized for all patients who are treated with Invisalign. Moreover, it has been argued that retrospective studies may not able to control patient cooperation.[16] Nevertheless, reviewing patient charts at the end of treatment to verify that they changed their aligners at regular time intervals and attended their appointments seems just as effective as the compliance logs used in other studies.

Furthermore, superimpositions were done on posterior teeth, which were assumed to be stable even though minimal movement was observed. Unfortunately, this was the best available option, because of the absence of stable anatomic structures in ClinCheck. Consequently, any movements detected were relative to the molars. The superimposition obstacle could be partially overcome with the use of cone-beam computed tomography. If these scans were available at both time points, a cranial-base superimposition would allow accurate measurement of the achieved movements. However, for the predicted movements, measurements would still be needed with ClinCheck.

Table II. Wilcoxon signed-rank test between predicted and achieved movements

Movement	*Median predicted*	*Median difference (predicted-achieved)*	*P value*
Maxillary central incisors horizontal (mm)	1.00	0.25	*
Maxillary lateral incisors horizontal (mm)	0.80	0.25	NS
Maxillary canines horizontal (mm)	1.15	0.20	*
Maxillary central incisors intrusion (mm)	1.00	1.50	*
Maxillary central incisors extrusion (mm)	1.35	−0.30	NS
Maxillary lateral incisors intrusion (mm)	0.50	1.10	*
Maxillary lateral incisors extrusion (mm)	0.90	−0.25	NS
Maxillary canines vertical (mm)	0.30	−0.10	NS
Maxillary intercanine width (mm)	2.05	0.45	*
Maxillary interpremolar width (mm)	1.45	0.25	NS
Maxillary central incisors rotation (°)	4.40	2.00	*
Maxillary lateral incisors rotation (°)	6.50	1.85	*
Maxillary canines rotation (°)	6.50	3.05	*
Maxillary premolars rotation (°)	3.40	0.90	*
Mandibular incisors horizontal (mm)	1.00	0.00	NS
Mandibular canines horizontal (mm)	1.00	0.20	NS
Mandibular incisors intrusion (mm)	1.10	0.80	*
Mandibular incisors extrusion (mm)	0.25	−0.30	NS
Mandibular canines vertical (mm)	0.70	0.30	*
Mandibular premolars vertical (mm)	0.20	0.00	NS
Mandibular intercanine width (mm)	1.85	−0.10	NS
Mandibular interpremolar width (mm)	1.25	0.00	NS
Mandibular incisors rotation (°)	7.75	1.85	*
Mandibular canines rotation (°)	11.40	2.45	*
Mandibular premolars rotation (°)	5.90	1.90	*

A negative sign indicates that the achieved value was greater than the predicted one.
NS, Not significant.
*Statistically significant difference ($P \leq 0.002$).

Attachments and interproximal reduction may impact the accuracy of various tooth movements, but the evidence is unclear.[15,17,19] In this study, it was assumed that the supervising orthodontist had enough experience to prescribe them appropriately, and no restrictions were applied.

In addition, all measurements were done at the incisal edges. Buccolingual and mesiodistal tipping and torque were not studied. Invisalign describes movements as translation and tipping with an arbitrary center of rotation. It is possible that the movements were expressed differently than predicted (ie, more tipping than translation); this would have an impact on the displacement of the incisal edge.

Finally, an important limitation of this study, and every other study of similar design to date, is that multiple teeth were used from the same patient. In reality, the movement of 1 tooth is not independent from the movement of adjacent teeth or the ones that are used as anchorage. Additionally, the components of tooth movement on different planes were analyzed individually, but actually there is only 1 resultant movement for each tooth. The ideal way to overcome this limitation would be to include only 1 movement of 1 tooth from every patient. However, that would require an enormous sample or fewer variables.

We failed to detect any major differences between predicted and achieved movements in the horizontal plane. The greatest difference was found in the maxillary intercanine width change. That is not surprising, since the maxillary canines have the longest roots and conical crown morphology with few undercuts to enhance aligner retention. Interpremolar expansion was accurate, but the average amounts of planned expansion were only 1.49 mm for the maxillary premolars and 1.76 mm for the mandibular premolars.

The most notable linear differences were found in vertical movements.[7] Intrusion in particular was the most unpredictable: linear movements had differences ranging from 0.8 to 1.5 mm. Especially for the maxillary central and lateral incisors, even though the planned movement was intrusion, the achieved movement was extrusion. This could be partly a result of the superimposition method. Invisalign has a bite-block effect, because 2 aligners of 0.38-mm width are interposed between posterior teeth throughout treatment. Unexpected intrusion of the molars would cause the incisors to appear extruded on the posttreatment models after superimposition. One more finding that supports this theory is that the achieved extrusion was often larger than predicted, even though the difference was not statistically significant.

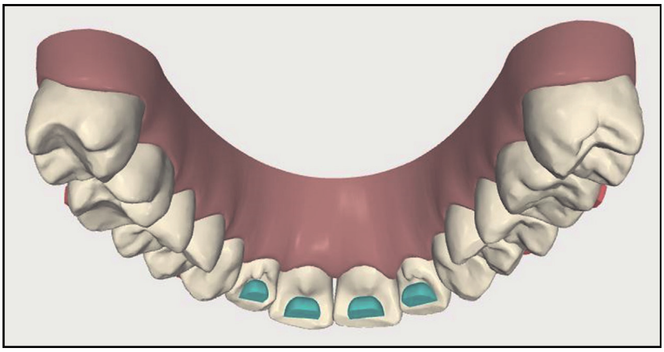

Fig 5. Bite ramps are projections of the aligners on the lingual surfaces of the maxillary incisors that disclude the posterior teeth (screenshot from ClinCheck).

Although achieving extrusion instead of intrusion may appear to be a flaw of this study, this finding should not be disregarded. The extrusion of incisors relative to the molars could have clinical significance. The bite-block effect may make deepbites more difficult and open bites easier to treat with Invisalign. This study included 3 patients with anterior open bites, 1 patient with a posterior open bite, and several ptients with deep-bites. Future research could focus on 1 or the other to obtain more clear results regarding the vertical effects of Invisalign. Anterior bite ramps (Fig 5) could prevent the bite-block effect, but they were used in only 2 patients in this sample. This feature of Invisalign may have a significant impact in deepbite correction and is worth studying separately.

All achieved rotations were significantly smaller than the predicted ones by different amounts. The median differences ranged from 0.9° to 3.05°. Kravitz et al[16] also found that rotations of the maxillary and mandibular canines were the most unpredictable of all anterior teeth. They suggested that overcorrection can be the solution for this problem only up to a certain point. If the overcorrection is too big, it will be like a bend on an archwire that is too strong to be engaged into the bracket slot. Also, overcorrections are not as simple for other types of movements, such as horizontal and vertical, and one must keep in mind possible side effects and occlusal interferences.

Although most previous studies expressed the accuracy of Invisalign in percentages, in this study we chose to focus on the size of the difference between the predicted and achieved movements. The reason for that was simply that a percentage gives less information about the movements that were studied and the differences that were found.

As mentioned before, all previous studies were published before the introduction of the SmartTrack material and the latest attachments as well as software updates. We hope that this study offers some valuable evidence regarding the accuracy of Invisalign in its current version.

Future research should focus on measuring fewer variables with a larger sample to obtain more reliable results.

CONCLUSIONS

No significant differences were detected between the predicted and achieved horizontal movements of teeth. However, the achieved rotations and vertical movements were significantly different than predicted.

Rotations of canines and intrusions of incisors were the most inaccurate movements, suggesting that overcorrection of these movements could decrease the need for refinement.

Due to the heterogeneity of the malocclusions and the small sample size, this study can be regarded as a pilot study, and further research is needed to validate our findings.

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PUBLICATION
III

Treatment outcome with orthodontic aligners and fixed appliances: a systematic review with meta-analyses

Papageorgiou S, Koletsi D, Iliadi A, Peltomaki T, Eliades T

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OXFORD

Systematic review

Treatment outcome with orthodontic aligners and fixed appliances: a systematic review with meta-analyses

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Summary

Background: The use of orthodontic aligners to treat a variety of malocclusions has seen considerable increase in the last years, yet evidence about their efficacy and adverse effects relative to conventional fixed orthodontic appliances remains unclear.
Objective: This systematic review assesses the efficacy of aligners and fixed appliances for comprehensive orthodontic treatment.
Search methods: Eight databases were searched without limitations in April 2019.
Selection criteria: Randomized or matched non-randomized studies.
Data collection and analysis: Study selection, data extraction, and risk of bias assessment was done independently in triplicate. Random-effects meta-analyses of mean differences (MDs) or relative risks (RRs) with their 95% confidence intervals (CIs) were conducted, followed by sensitivity analyses, and the GRADE analysis of the evidence quality.
Results: A total of 11 studies (4 randomized/7 non-randomized) were included comparing aligners with braces (887 patients; mean age 28.0 years; 33% male). Moderate quality evidence indicated that treatment with orthodontic aligners is associated with worse occlusal outcome with the American Board of Orthodontics Objective Grading System (3 studies; MD = 9.9; 95% CI = 3.6–16.2) and more patients with unacceptable results (3 studies; RR = 1.6; 95% CI = 1.2–2.0). No significant differences were seen for treatment duration. The main limitations of existing evidence pertained to risk of bias, inconsistency, and imprecision of included studies.
Conclusions: Orthodontic treatment with aligners is associated with worse treatment outcome compared to fixed appliances in adult patients. Current evidence does not support the clinical use of aligners as a treatment modality that is equally effective to the gold standard of braces.
Registration: PROSPERO (CRD42019131589).

Introduction

Rationale

The use of sequential clear aligners to treat malocclusion has seen a remarkable surge in the last decades and, fueled by aggressive marketing campaigns from manufacturers, a growing interest has been reported for such methods for invisible orthodontics, especially among adult patients (1, 2). A survey of Australian orthodontists in 2013 indicated that 73% of responders had used aligners to treat at least one case in the last year, with a median of eight aligner cases (3). A similar survey among Irish orthodontists in 2014 reported that 19% of them often used aligners to treat adult patients (4). A large 2014 survey among orthodontic specialists in the States (5) revealed that 89% of them had treated at least one case with aligners (compared to 76% in 2008) with a median of 22 cases/year with aligners (compared to 12 cases/year in 2008), but only few orthodontists used aligners for premolar extraction cases (9–18%). Additionally, another survey among members of the European Aligner Society indicated that 45% of orthodontists believed that aligners limit orthodontic treatment outcomes (even though the respective percentage among general dentists was only 5%) (6). These data might indicate that the initial surge of aligner treatment during its early years of fame might have now given its place to a more mature evaluation of this treatment modality, based on long-term outcomes.

Contrary to many medical fields, it is common place in orthodontics that novel marketed products and treatment approaches are clinically adopted based on advertisement policies, apparently without the appropriate clinical evidence to back any claims by the manufacturers (7, 8). In any case, it is imperative that alternative treatment methods offered to orthodontic patients are based on both the doctor's clinical expertise and solid evidence on the clinical performance of this modality. Ideally, treatment decisions should be based on well-designed and -reported comparative clinical trials on human patients and systematic reviews/meta-analyses thereof, after meticulous considerations of treatment efficacy and adverse effects (9, 10). Ample empirical evidence has now been gathered about the importance of proper study design and methodological characteristics that may result in bias (11–16).

In the last decade several systematic reviews of clinical studies comparing orthodontic aligners with fixed appliances have emerged (17–27). However, they all present methodological issues that may introduce bias and hamper their ability to draw robust evidence-based recommendations, including: lack of an a priori design/pre-registered protocol (18–21, 25, 26), language bias (19, 21, 24), inclusion of non-randomized studies with uncontrolled confounding (18, 19, 21, 24–27), inadequate handing of the studies' risk of bias (18–21, 24–27), lack of quantitative data synthesis (meta-analysis) (18, 19, 21, 24, 26, 27), improper data synthesis methods (20, 25), and being outdated (18–20). Therefore, it is important that clinical practice is informed by a critical appraisal of currently available studies according to the principles of evidence-based medicine.

Objective

The aim of this systematic review was to critically assess the evidence derived from randomized clinical trials (RCTs) on humans undergoing orthodontic treatment to answer the question: Is there a difference in the treatment outcome with aligners compared to fixed appliances for comprehensive orthodontic treatment?

Materials and methods

Protocol and registration

This review's protocol was made a priori, registered in PROSPERO (CRD42019131589), and all post hoc changes were appropriately noted (Supplementary Table 1). This review is conducted and reported according to Cochrane Handbook (28) and PRISMA statement (29), respectively.

Eligibility criteria

According to the Participants-Intervention-Comparison-Outcome-Study design (PICOS) schema and due to the scarcity of RCTs on this subject, included were RCTs and non-randomized clinical studies on human patients of any age, sex, ethnicity, or malocclusion comparing full-arch orthodontic treatment with aligners and fixed appliances. No limitations concerning language, publication year, or status were applied. Due to the scarcity of randomized trials on the subject, non-randomized studies were also included, with the requirement that the populations to be compared were matched regarding baseline malocclusion severity with objective measures like the Peer Assessment Rating (PAR) index (30) or the Discrepancy Index (DI) (31) from the American Board of Orthodontics (ABO). In particular, matching at the design stage was a pre-requisite for study inclusion, to eliminate baseline confounding due to potential risk factors that might present a bearing on the outcome of interest. Matching was judged adequate when the Cohen's d for PAR or ABO DI between aligner and fixed appliance group at baseline was up to 0.3. Excluded were animal studies, case reports/series, non-clinical studies, and cross-sectional studies. Excluded were also studies without comprehensive orthodontic treatment, without two distinct treatment groups for aligners/fixed appliances, studies on previously treated patients, and studies without any outcome eligible for this review. The primary outcome for this review was the outcome of comprehensive orthodontic treatment judged with objective and reliable measures like the PAR index and the ABO's Objective Grading System (ABO-OGS) for dental casts and panoramic radiographs (32). Secondary outcomes included treatment duration, as well as adverse effects like loss of periodontal support, External Apical Root Resorption (EARR), gingival recession, and proclination of the lower incisors during treatment.

Information sources and search

Eight electronic databases were searched systematically without any restrictions for publication date, language, or type from inception up to 25 April 2019 (Supplementary Table 2), while Directory of Open Access Journals (DOAJ), Digital Dissertations, metaRegister of Controlled Trials, WHO, and Google Scholar, as well as the reference/citation lists of eligible articles or existing systematic reviews were manually searched for any additions.

Study selection

Three authors (SNP, DK, AI) screened the titles and/or abstracts of studies retrieved from the searches to identify articles that potentially meet the inclusion criteria, before moving to their full-texts. Any differences between the two reviewers were resolved by discussion with the last author (TE).

Data collection process and items

Data collection from the identified reports was conducted using pre-defined and piloted forms covering: (a) study characteristics (design, clinical setting, country), (b) patient characteristics (age, sex), (c) malocclusion and treatment characteristics, (d) appliance type—including number of aligners and amount of Interproximal Reduction (IPR) performed, (e) follow-up period, and (f) outcome details. Data were extracted by three authors (SNP, DK, AI) with the same way to resolve discrepancies as above.

Risk of bias of individual studies

The risk of bias of included studies was assessed according to Cochrane guidelines with the RoB 2.0 tool for randomized trials (33) and the ROBINS-I ('Risk Of Bias In Non-randomised Studies—of Interventions') tool for non-randomized studies (34). Assessment of the risk of bias within individual trials was likewise performed independently by three authors (SNP, DK, AI), with the same way to resolve discrepancies consulting the last author (TE).

Data synthesis and summary measures

An effort was made to include all existing trials in the analysis; where data were missing, they were calculated by ourselves, requested from the authors or calculated from graphs (Supplementary Table 2). As the outcome of orthodontic treatment is bound to be affected by patient and treatment-related characteristics, a random-effects model was deemed appropriate to calculate the average distribution of true effects, based on clinical and statistical reasoning (35), and a restricted maximum likelihood random-effects model was used according to recent guidance (36). Mean differences (MDs) for continuous outcomes and relative risks (RRs) for binary outcomes and their corresponding 95% confidence intervals (CIs) were calculated as effect sizes. Statistically significant RRs were translated into Numbers Needed to Treat (NNTs) to gauge their clinical relevance.

The extent and impact of between-study heterogeneity was assessed by inspecting the forest plots and by calculating the τ^2 (absolute heterogeneity) or the I^2 statistics (relative heterogeneity). I^2 defines the proportion of total variability in the result explained by heterogeneity, and not chance, and we considered arbitrarily I^2 over 75% to represent considerable heterogeneity, while also considering the heterogeneity's direction (localization on the forest plot) and uncertainty intervals around heterogeneity estimates (37). Ninety-five percent predictive intervals were calculated for meta-analyses of at least three trials to incorporate existing heterogeneity and provide a range of possible effects for a future clinical setting, which are crucial for the correct interpretation of random-effects meta-analyses (38).

Additional analyses and risk of bias across studies

Possible sources of heterogeneity were a priori planned to be sought through subgroup analyses and random-effects meta-regression in meta-analyses of at least five trials but could ultimately not be performed (Supplementary Table 2). Likewise, reporting biases were planned but ultimately not assessed, due to the limited number of meta-analyzed trials.

The overall quality of meta-evidence (i.e. the strength of clinical recommendations) was rated using the Grades of Recommendations, Assessment, Development and Evaluation (GRADE) approach (39) following recent guidance on combining randomized with non-randomized studies (40) and summary of findings tables were constructed using the improved format proposed by Carrasco-Labra *et al.* (40). The minimal clinically important, large and very large effects were defined as half, one and two standard deviations of the post-treatment response (for continuous outcomes) and RRs of 1.5, 2.0, and 5.0 (for binary outcomes) (42, 43). The produced forest plots were augmented with contours denoting the magnitude of the observed effects to assess heterogeneity, clinical relevance, and imprecision (44).

Robustness of the results was planned a priori to be checked with sensitivity analyses based on (a) inclusion/exclusion of non-randomized studies, (b) inclusion/exclusion of trials with methodological shortcomings, and (c) improvement of the GRADE classification. In the end, only one sensitivity analysis excluding non-randomized studies could be conducted.

All analyses were run in Stata version 14.0 (StataCorp LP, College Station, TX) by one author (SNP) and the dataset was openly provided (45). All *P* values were two-sided with $\alpha = 5\%$, except for the test of between-studies or between-subgroups heterogeneity where α-value was set as 10% (46).

Results

Study selection

The electronic literature search yielded 1376 results, while another seven were manually identified from the reference/citation lists of identified papers (Figure 1). After duplicate removal and screening the titles/abstracts of identified reports, the full texts of 343 papers were checked against the eligibility criteria (Supplementary Table 3). Ultimately, 11 papers pertaining to 11 unique studies (4 randomized and 7 retrospective non-randomized) were finally included, which were published as journal papers of dissertation/theses.

Study characteristics

The included studies were conducted in university clinics (n = 6; 55%), private practices (n = 4; 36%), or hospitals (n = 1; 9%) and originated from six different countries (Canada, China, Ireland, Italy, South Korea, and the United States of America) (Table 1). A total of 446 and 443 patients were treated with aligners and fixed appliances, respectively, with a median total sample of 66 patients per included study (range 19–200 patients per study). Out of the seven studies reporting on patient sex, 215 of the 661 patients in total were male (33%), while the mean patient age out of the nine studies reporting this was 28.0 years.

As far as complexity of the treated cases is concerned, only six studies (55%) reported this with either the PAR index (n = 3; 27%) or the ABO DI (n = 3; 27%). Eight of the studies (73%) performed non-extraction treatment, one study (9%) both extraction and non-extraction treatment, and one study (9%) extraction treatment. The majority of studies (9/11 studies; 82%) reported on conventional comprehensive treatment, while one study (9%) reported on orthodontic treatment of patients with history of periodontal disease and one study (9%) reported on combined orthodontic/orthognathic treatment. Details of the aligner treatment were only partly reported among the included studies with only two studies (18%) reporting the number of aligners, four studies (36%) reporting on 'refinement' rate (i.e. the mid-course re-evaluation and planning of additional aligners), and two studies (18%) on the actual amount of interproximal enamel reduction performed during treatment in both groups.

The included studies reported on a wide spectrum of treatment outcomes, with only three studies reporting on the complete ABO-OGS score including all eight components, as well as failure of the case to pass the ABO criteria for adequate occlusal results (ABO-OGS score < 30 points). One study reported on the ABO-OGS score of seven out of eight components (excluding root angulation) and also excluded scoring the second molars without any justification. One study also reported solely on two of the eight ABO-OGS components—namely marginal ridges and buccolingual inclination. Three studies used the PAR index and reported either post-treatment PAR scores or PAR reductions. Eight studies reported on treatment duration, though considerable variation in the reported results was seen. Finally, single studies reported on periodontal probing depth, alveolar bone loss, EARR, lower incisor inclination, and gingival recessions.

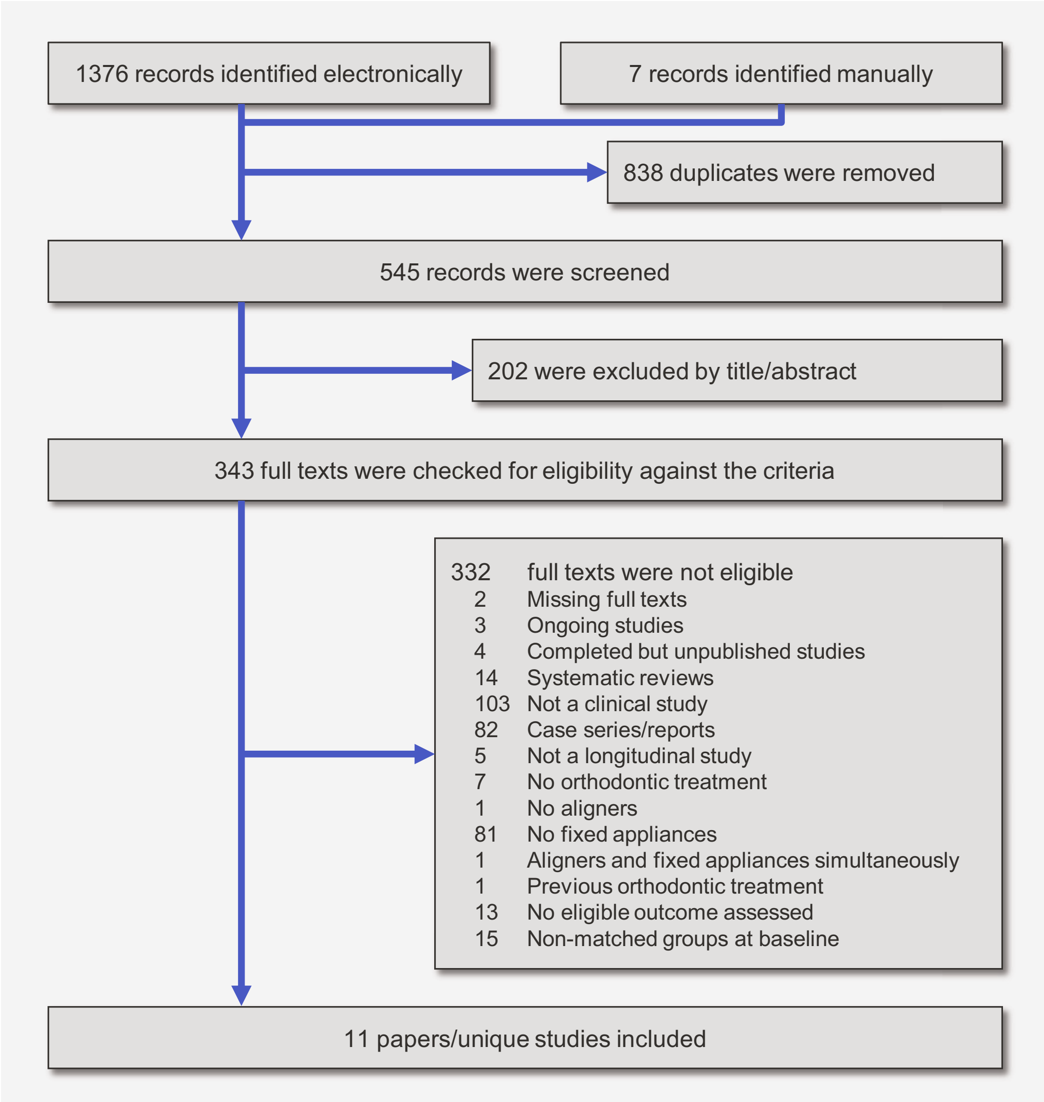

Figure 1. PRISMA flow diagram for the identification and selection of eligible studies in this review.

Risk of bias within studies

The included randomized trials presented several issues that increased their risk for bias (Supplementary Table 4). Two trials were in high risk of bias due to problems in the randomization process, deviations from intended interventions, missing outcome data, and outcome measurement. The remaining two trials were in low risk of bias, except from the fact that no a priori trial protocol could be found to rule out selective reporting. The included non-randomized studies were in considerably higher risk of bias (Supplementary Table 5), with five of them presenting moderate risk of bias, one of them serious risk of bias, and one of them critical risk of bias. Their main shortcomings pertained to confounding, selection of participants into the study, deviations from intended interventions, outcome measurement, and selection of the reported result.

Data synthesis

For all included studies the data reported in the paper were used, while for one study without matching (51) the author provided raw data that were used to extract a matched sub-sample to include (Supplementary Table 6). The results of all individual trials and the results of the meta-analyses of at least two studies are found in Supplementary Table 7 and Table 2.

Table 1. Characteristics of included studies.

Study	Design; setting; country*	Patients (M/F); age**	Malocclusion/Tx	Appliance	Aligners/refinement/IPR (mm)	FU (mos)	Outcome
Abbate 2015 (47)	RCT; Uni; ITA	AL: 25 (NR); (10–18) FX: 22 (NR); (10–18)	NR/Non-Ex	AL: Invisalign® FX: Labial CLB	NR/NR/NR	BL, 3.0, 6.0, 9.0, 1 2.0 mos in Tx	PPD
Djeu 2005 (48)	rNRS; Pract; USA	AL: 48 (NR); 33.6 FX: 48 (NR); 23.7	DI: 19.3; Ex and Non-Ex	AL: Invisalign® FX: Labial CLB (TE)	NR/NR/allowed	BL, END	ABO-OGS_8; TxDur
Fetouh 2008 (49)	rNRS; Pract; USA	AL: 33 (NR); NR FX: 33 (NR); NR	Cl. I; mild crowding and overbite; DI: 3.22/Non-Ex	AL: Invisalign® FX: Labial CLB	NR/NR/NR	BL, END	ABO-OGS_7
Gu 2017 (50)	rNRS; Pract; USA	AL: 48 (16/32); 26.0 FX: 48 (18/30); 22.1	PAR: 21.8; compliant/Non-Ex	AL: Invisalign® FX: Labial CLB (SW)	NR/38%/NR	BL, END	PAR; TxDur
Han 2015 (51)	rNRS; Uni; KOR	AL: 10 (2/8); 51.2FX: 9 (4/5); 47.3	Previous PerioDis; DI: 4.4/Non-Ex	AL: NR FX: Labial CLB	NR/NR/allowed	BL, END	ABL; PPD; TxDur
Hennessy 2016 (52)	RCT; Hosp; IRL	AL: 20 (6/14); 29.1 FX: 20 (7/13); 23.7	Mild crowding/Non-Ex	AL: Invisalign ® FX: Labial SLB (MBT)	18 ALs/allowed/ AL:FX 1.9:1.5	BL, END	IMPA; TxDur
Lanteri 2018 (53)	rNRS; Pract; ITA	AL: 100 (30/70); 28.0 FX: 100 (30/70); 25.0	PAR: 23.3/Non-Ex	AL: Invisalign® FX: Labial SLB (MBT)	43 ALs***/37%/ AL:FX 1.3:1.5	BL, END, 24.0 mos Post-Tx	PAR; RetFail; GingRec
Li 2015 (54)	RCT; Uni; CHN	AL: 76 (27/45); 35.2 FX: 76 (27/45); 32.2	DI: 27.4/Ex	AL: Invisalign® FX: Labial CLB	NR/NR/allowed (AL)	BL, END	ABO-OGS_8; TxDur
Preston 2017 (55)	RCT; Uni; USA	AL: 22 (10/12); 27.8 FX: 22 (7/15); 25.4	Cl. I; mild crowding/ Non-Ex	AL: Invisalign® FX: Labial CLB (ALX)	NR/100% (2 refinements)/NR	BL, END, 1.0, 6.0 mos Post-Tx	ABO-OGS_2; TxDur; contact areas
Robitaille 2016 (56)	rNRS; Uni; CAN	AL: 24 (11/13); 29.8 FX: 25 (6/19); 23.4	DI: 31.5/orthognathic surgery	AL: Invisalign® FX: Labial CLB	NR/NR/NR	BL, END	ABO-OGS_8; TxDur
Yi 2018 (57)	rNRS; Uni; CHN	AL: 40 (9/31); 21.8 FX: 40 (11/29); 23.3	PAR: 22.6/Non-Ex	AL: NR FX: Labial CLB	NR/65%/NR	BL, END	PAR; TxDur; EARR

ABL: alveolar bone level, ABO-OGS: American Board of Orthodontists Objective Grading System (number of components assessed given in subscript), AL: aligner, ALX: Alexander technique, BL: baseline, Cl: (Angle's) Class, CLB: conventionally ligated brackets, DI: discrepancy index, EARR: external apical root resorption, END: end of comprehensive treatment, Ex: extraction, FU: follow-up, FX: fixed appliance, GingRec: gingival recession, Hosp: hospital, IMPA: inclination of lower incisors to mandibular plane, IPR: interproximal enamel reduction, M/F: male/female, MBT: MacLaughlin–Bennet–Trevisi prescription, mo: month, NR: not reported, PAR: peer assessment rating, PerioDis: periodontal disease, PPD: periodontal probing depth, Pract: private practice/clinic, RCT: randomized clinical trial, SLB: self-ligating bracket, SW: straightwire, TE: tip-edge, Tx: treatment, TxDur: treatment duration, Uni: university clinic.

*Countries given with their alpha-3 codes.

**Patient age is given either as mean (one value in without parenthesis) or if mean isn't reported as range (two values in parenthesis).

***Including refinement aligners.

Table 2. Results of random-effects meta-analyses for eligible outcomes with at least two contributing studies comparing aligners to fixed appliances.*

Outcome*	n	Effect	P	I^2 (95% CI)	tau² (95% CI)	95% prediction
ABO-OGS total score	**2**	**MD: 13.38 (9.45, 17.31)**	**<0.001†**	**0% (0%, 98%)**	**0 (0, 371.98)**	**NC**
ABO-OGS failure (score>30)	2	RR: 1.63 (1.24, 2.13)	<0.001†	0% (0%, 99%)	0 (0, 4.47)	NC
ABO-OGS component 1: alignment	2	MD: 2.60 (-0.48, 5.69)	0.10	89% (24%, 100%)	4.40 (0.18, 622.82)	NC
ABO-OGS component 2: marginal ridges	2	MD: 0.60 (-0.22, 1.43)	0.15	0% (0%, 98%)	0 (0, 21.95)	NC
ABO-OGS component 3: buccolingual inclination	2	MD: 1.14 (0.21, 2.07)	0.02†	0% (0%, 99%)	0 (0, 59.04)	NC
ABO-OGS component 4: occlusal contacts	**2**	**MD: 4.45 (2.72, 6.18)**	**<0.001†**	**0% (0%, 98%)**	**0 (0, 85.36)**	**NC**
ABO-OGS component 5: occlusal relationship	2	MD: 1.39 (-0.12, 2.89)	0.07	28% (0%, 99%)	0.33 (0, 148.14)	NC
ABO-OGS component 6: overjet	2	MD: 2.61 (1.29, 3.93)	<0.001†	0% (0%, 98%)	0 (0, 61.18)	NC
ABO-OGS component 7: interproximal contacts	2	MD: 0.02 (-0.17, 0.21)	0.83	0% (0%, 98%)	0 (0, 2.71)	NC
ABO-OGS component 8: root angulation	2	MD: 0.87 (0.46, 1.28)	<0.001†	0% (0%, 98%)	0 (0, 6.63)	NC
PAR post-Tx	2	MD: -0.03 (-2.02, 1.96)	0.98	83% (0%, 100%)	1.72 (0, 258.55)	NC
PAR reduction via Tx	3	MD: -1.76 (-3.62, 0.10)	0.06	41% (0%, 96%)	1.13 (0, 42.78)	-19.88, 16.36
PAR great improvement (reduction>30)	2	RR: 0.72 (0.40, 1.28)	0.26	66% (0%, 100%)	0.12 (0, 22.56)	NC
Treatment duration (months)	7	MD: -0.55 (-3.73, 2.63)	0.73	94% (82%, 99%)	16.25 (4.74, 73.67)	-11.72, 10.62

ABO-OGS, American Board of Orthodontists Objective Grading System; CI, Confidence Interval; MD, Mean Difference; n, number of contributing studies; NC, Non-Calculable; PAR, Peer Assessment Rating; RR, Relative Risk.
†statistically significant findings at the 5% level.
*with bold are given meta-analyses being both statistically significant and clinically relevant – judged as having an effect being at least equal to the average standard deviation of the control (fixed appliance) group across included studies or a relative risk of at least 2.

Fourteen different meta-analyses could be conducted pertaining to the review's primary outcome (ABO-OGS scores), PAR scores, and treatment duration. A meta-analysis of three studies indicated that treatment with aligners was associated with significantly worse ABO-OGS scores compared to braces (MD = 9.9 points greater; 95% CI = 3.6–16.2 points greater; P = 0.002), which was also clinically relevant (Table 3; Figure 2). Considerable heterogeneity was seen among the three included studies (I^2 = 84%), which meant that several patient-related or treatment-related factors might play a role in the actual final occlusal result. However, existing heterogeneity influenced only the precise calculation of the difference between aligners and fixed appliances, as one study indicated a moderate difference and the other two indicated a large one. It did not however influence the direction of the effect, as all three studies showed that fixed appliances were significantly associated with better treatment results than aligners.

Additionally, patients treated with aligners were significantly more likely to be finished to an unacceptable quality according to the ABO standards and fail the ABO examination criteria (ABO-OGS score > 30) compared to those treated with braces (3 studies; RR = 1.6; 95% CI = 1.2–2.0; P < 0.001; Table 3; Supplementary Figure 1). No considerable heterogeneity across studies was seen, which reported a small to moderate increase in the rate of suboptimal finishing quality. On absolute terms these corresponded to ABO 'fail rates' of 60.6% and 38.9% for aligners and braces, respectively (Supplementary Figure 2). This is translated to an NNT of 5, which means that every fifth case treated with aligners instead of fixed appliances would fail the ABO examination, but would get a 'passing' grade if it was treated with fixed appliances, which is a potentially clinically relevant effect.

Looking at the comparative performance for each separate component of ABO-OGS between aligners and braces gives a more precise image about the occlusal aspects mostly affected by the treatment modality (Table 3; Figure 3). Overall, meta-analyses of three studies indicated that five of the eight aspects of the occlusion were finished significantly worse with aligners than with fixed appliances: buccolingual inclination (MD: 0.8 point; 95% CI: 0.5–1.1 point; P < 0.001), occlusal contacts (MD: 3.1 points; 95% CI: 0.6–5.6 points; P = 0.02), occlusal relationship (MD: 1.0 point; 95% CI: 0.6–1.4 points; P < 0.001), overjet (MD: 1.8 points; 95% CI: 0.6–3.0 points; P = 0.002), and root angulation (MD: 0.8 point; 95% CI: 0.5–1.1 point; P < 0.001). Looking carefully at the effect magnitude it is obvious that the clinical relevance for each separate criterion is questionable, as small to moderate differences between aligners and braces are seen on average. However, when adding all these differences for each criterion, a clinically relevant worse treatment outcome is seen with aligners overall.

Looking at the occlusal outcome of treatment through meta-analyses using the PAR index gives a slightly different picture (Table 3). Overall, no statistically significant difference between aligners and braces was detected either by post-treatment absolute values (2 studies; P = 0.98) or by PAR reduction (3 studies; P = 0.06). Likewise, no difference in the proportion of patients experiencing a great improvement in their PAR scores through treatment (PAR reduction of at least 22 points or PAR score of 0 post-treatment) was seen (2 studies; P = 0.26).

Considerable variation was seen in the effect of treatment modality on treatment duration. Meta-analysis of seven studies indicated that on average no definite conclusions can be drawn regarding treatment duration with either aligners or fixed appliances (MD: –0.6 month; 95% CI: –3.7 to 2.6 months; P = 0.73). Extreme

Table 3. Summary of findings table according to the GRADE approach.

Outcome [follow-up] Studies (patients)	Relative effect (95% CI)	Anticipated absolute effects (95% CI) Fixed appliance**	Aligners	Difference in aligner group	Quality of the evidence (GRADE)*	What happens with aligners
ABO-OGS score [post Tx] 145 patients (2 studies)	—	29.9 pts	—	13.4 pts greater (9.5 to 17.3 greater)	⊕⊕⊕○ moderate[c,d] due to bias	Probably leads to worse finishing quality (higher ABO-OGS scores)
Unacceptable finishing quality (ABO-OGS score>30 pts) [post Tx] 145 patients (2 studies)	RR 1.6 (1.23 to 2.13)	48.0%	78.2% (59.0%–100.0%)	30.2% more (11.0% to 52.0% more)	⊕⊕⊕○ moderate[c] due to bias	Probably leads to more patients with unacceptable finishing quality
PAR reduction [post Tx] 376 patients (3 studies)	—	19.5 pts	—	1.8 pts less (3.6 less to 0.1 more)	⊕⊕○○ low[e] due to bias	Little to no difference in treatment efficacy (smaller reduction in PAR scores)
Great improvement in PAR (PAR reduction>30 pts) [post Tx] 296 patients (2 studies)	RR 0.7 (0.40 to 1.28)	46.0%	33.0% (18.5%–58.8%)	13.0% less(27.5% less to 12.8% more)	⊕⊕○○ low[e] due to bias	Little to no difference in patients with great improvement in PAR scores
Treatment duration [post Tx] 607 patients (7 studies)	—	19.6 mos	—	0.6 mo shorter (3.7 shorter to 2.6 longer)	⊕○○○ very low[f,g] due to bias, inconsistency	Too heterogenous response to synthesize across studies
EARR as % of anteriors' root length [post Tx] 80 patients / 640 teeth (1 study)	—	7.0%	—	1.8% less (1.3% to 2.4% less)	⊕⊕○○ low[e] due to bias	Might lead to greater EARR
Inclination of lower incisors [near Tx end] 44 patients (1 study)	—	5.3°	—	1.9° less (4.1° less to 0.3° more)	⊕⊕○○ low[h,i] due to bias, imprecision	Little to no difference in lower incisor inclination
Gingival recession [2 years post Tx] 158 patients (1 study)	RR 0.9 (0.31 to 2.68)	8.0%	7.2% (2.5%–21.4%)	0.8% less(5.5% less to 13.4% more)	⊕⊕⊕○ moderate[c] due to bias	Little to no difference in gingival recession

Intervention: comprehensive orthodontic treatment with thermoplastic aligners versus fixed appliances / Population: adolescent or adult patients with any kind of malocclusion / Setting: university clinics, private practice, hospital (Canada, China, Ireland, Italy, USA).

[a] Response in the control group is based on average response of included studies (random-effects meta-analysis).

[b] Starts from "high"

[c] Downgraded by one level for bias due to the inclusion of non-randomized studies with moderate risk of bias

[d] Potentially great effect observed (larger than one average standard deviation), but no upgrading due to residual confounding.

[e] Downgraded by two levels for bias due to the inclusion of non-randomized studies with critical / serious risk of bias.

[f] Downgraded by two levels for bias due to the inclusion of randomized trials with high risk of bias and non-randomized studies with serious/critical risk of bias.

[g] Downgraded by one level due to inconsistency; great variability is seen among included studies with significant studies arranged on both sides of the forest plot (confident signs of heterogeneity that influence our decision about which treatment is shorter, which precludes calculating an average effect)

[h] Downgraded by one level for bias due to the inclusion of a randomized trial with high risk of bias.

[i] Downgraded by one levels for imprecision due to the inclusion of an inadequate sample.

ABO-OGS, American Board of Orthodontists Objective Grading System; CI, confidence interval; EARR, external apical root resorption; GRADE, Grading of Recommendations Assessment, Development and Evaluation; PAR, peer assessment rating; pt, point; Tx, treatment.

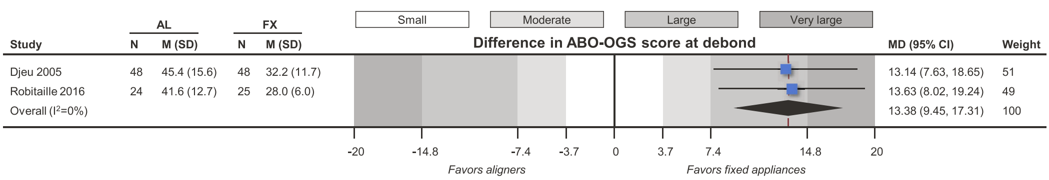

Figure 2. Contour-enhanced forest plot on the comparison of total ABO-OGS scores post-treatment between aligners and fixed appliances. ABO-OGS, American Board of Orthodontists Objective Grading System; AL, aligner; CI, confidence interval; FX, fixed appliance; M, mean; MD, mean difference; N, number of patients; SD, standard deviation. Contours correspond to different effect magnitude and the red dotted line corresponds to 95% random-effects prediction.

heterogeneity was seen across studies (I^2 = 94%), which makes the ability to synthesize existing studies into a single estimate questionable (Figure 4). Specifically, two studies reported statistically significant reduction in treatment duration with aligners, two studies reported statistically significant increase in treatment duration with aligners, while the remaining three studies did not find statistically

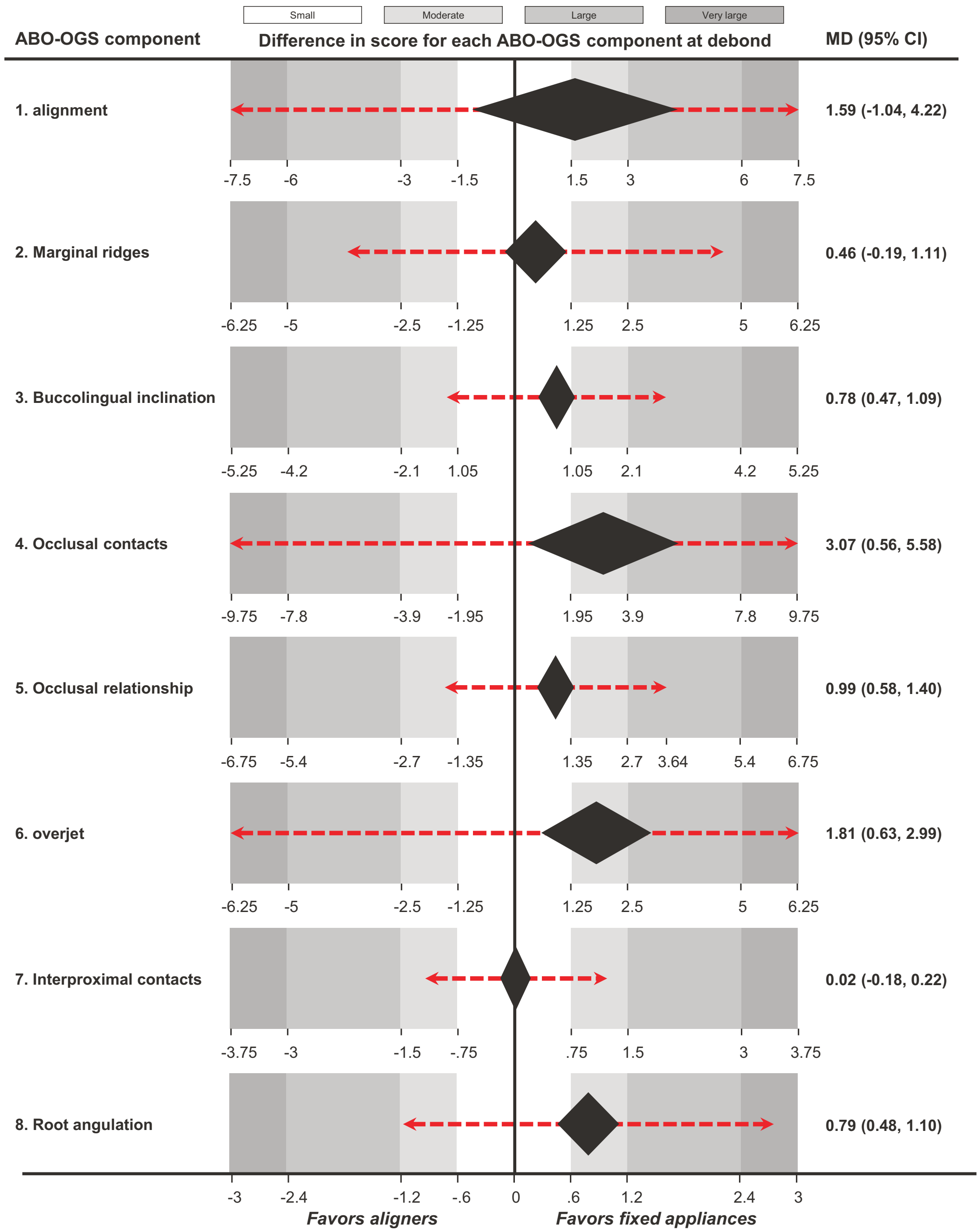

Figure 3. Composite contour-enhanced forest plot illustrating the summary results of 8 meta-analyses (each with 3 studies and 297 patients) for the comparison of each separate ABO-OGS component between orthodontic aligners and fixed appliances. ABO-OGS, American Board of Orthodontists Objective Grading System; CI, confidence interval; MD, mean difference. Contours correspond to different effect magnitude and the red dotted lines correspond to 95% random-effects predictions.

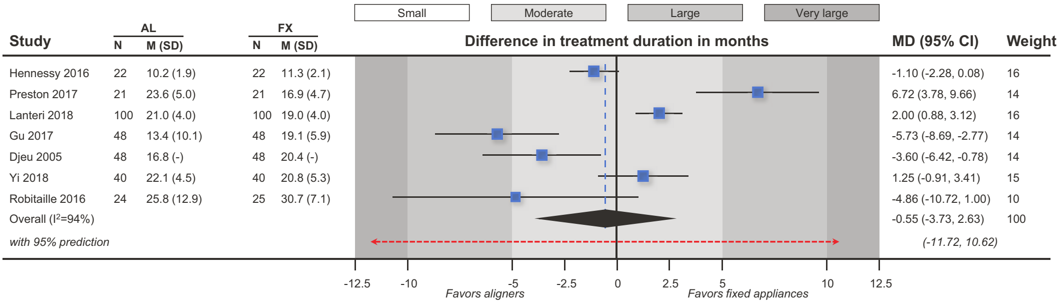

Figure 4. Contour-enhanced forest plot on the comparison of treatment duration in months between aligners and fixed appliances. AL, aligner; CI, confidence interval; FX, fixed appliance; M, mean; MD, mean difference; N, number of patients; SD, standard deviation. Contours correspond to different effect magnitude and the red dotted line corresponds to 95% random-effects prediction.

significant differences. Furthermore, exclusion of a study assessing combined orthodontic/orthognathic treatment (56) instead of only orthodontic treatment did not improve the results (6 studies; MD: −0.1 month; 95% CI: −3.5 to 3.4 months; I^2 = 95%). Nor was the situation improved by limiting the meta-analysis to only randomized trials (2 studies; MD: 2.69 months; 95% CI: −5.0 to 10.4 months; I^2 = 96%) or to only studies with non-extraction treatment (5 studies; MD: 0.6 month; 95% CI: −3.2 to 4.4 months; I^2 = 96%). Therefore, it is logical to assume that treatment duration is influenced by additional confounding variables and that the choice of appliance alone does not have a consistent influence on treatment duration.

Results of individual studies

Additionally, several outcomes were assessed by single studies that provide only limited insights (Supplementary Table 7). Results of a single study (50) indicated that aligners were worse in terms of reduction for the PAR component for upper anteriors (MD: −1.0 point; 95% CI: −1.9 to −0.1 point; P = 0.02) and overbite (MD: −1.0 point; 95% CI: −1.9 to −0.2 points; P = 0.02) compared to braces. The results of a single study (50) indicated that aligners were more efficient in terms of PAR reduction/month of treatment compared to fixed appliances (MD: 0.4 point/month; 95% CI: 0.1–0.7 point/month; P = 0.01). However, as the same study reported that aligners were overall associated with smaller reductions in the PAR scores than fixed appliances, looking at the PAR reduction/month might be misleading.

As far as adverse effects of treatment are concerned, a single identified study on EARR (57) reported that significantly smaller percentage of the incisors' root was resorbed during treatment compared to fixed appliances (MD: −1.8%; 95% CI: −2.4% to −1.3%; P < 0.001; Table 4). The same was seen for the various subgroups according to tooth type (central versus lateral incisor) and jaw (maxilla versus mandible), but the effect magnitude was on average very small and probably of no clinical relevance. Additionally, treatment with aligners was not associated in a single included study (52) with significantly lower proclination of the lower incisors compared to fixed appliances (P = 0.10). However, it must be noted that a very small sample was included, which makes the study probably underpowered to identify such a small difference of 1.9° between groups, if it really exists. Furthermore, no significant difference in the development of gingival recessions 2 years after treatment with aligners or fixed appliances was seen in another single study (MD: 0.9; 95% CI: 0.3–2.7; P = 0.86) (53).

Finally, limited evidence on the effect of appliance choice on loss of periodontal attachment was provided by a single identified study (51), which assessed orthodontic alignment of anterior teeth in adult patients with previous history of treated periodontal disease and found no differences between aligners and braces for periodontal probing depth (P = 1.00) or alveolar bone levels (P = 0.69). On the other side, fixed appliances were significantly quicker repositioning the patients' migrated anterior teeth compared to aligners (3.9 versus 6.0 months; MD: −2.1 months; 95% CI: −3.7 to −0.5 months; P = 0.01).

Additional analyses, risk of bias across studies, and quality of evidence

Several subgroup analyses, meta-regressions, and assessments for reporting biases were originally planned in the review's protocol, but could ultimately not be performed due to limited data and inadequate reporting (Supplementary Table 1).

The quality of evidence for the seven meta-analyses ranged from high to very low, as methodological limitations introducing bias, inconsistency, and imprecision were identified on some cases (Table 3). The two meta-analyses with significant differences in the ABO-OGS scores were supported by evidence of moderate quality, which indicates that these results are likely to be close to the estimate of the true effect. A GRADE rating of low was assigned to the significant difference in EARR, which however might be markedly different from the estimate of the true effect. Finally, the remaining five non-significant meta-analyses were supported by evidence of moderate to very low quality. The main reason for downgrading the quality of evidence pertained to the inclusion of non-randomized studies with serious/critical methodological issues that most probably introduce bias. This was especially seen in the retrospective study of Gu *et al.* (50) that selectively reported data from what might be regarded as 'good' cases, while excluding patients with issues of compliance or oral hygiene. This means that further research in terms of well-designed studies is very likely to have an important impact, which is likely to change our current estimates of effect.

Sensitivity analysis

The sensitivity analyses by omitting non-randomized studies indicated relative robustness of the results (Supplementary Table 8), apart from the observed reduced statistical power of the sensitivity analyses, which was expected after omitting trials.

Discussion

Summary of evidence

The current systematic review summarizes evidence from randomized trials and matched non-randomized studies on treatment outcome with orthodontic aligners or braces. Out of the initially identified 1376 hits from the literature search, 11 trials (involving 887 patients) were ultimately included.

Robust evidence from meta-analyses of overall ABO-OGS scores, individual ABO-OGS components, and proportion of treated cases with 'acceptable' finishing quality (ABO-OGS score < 30) indicated that treatment with aligners is associated with worse treatment outcome compared to braces (Table 2). It has been previously reported that it is considerably more difficult to control root movement with aligners compared to fixed appliances, especially without the use of attachments (2, 57, 58). Root movement is presumably better facilitated by adding ellipsoid precision attachments that can produce couples (2), which remains to be tested experimentally. On the other side, three ABO-OGS components (alignment, marginal ridges, and interproximal contacts) gave very similar results for both modalities. This is not surprising, since aligners are known to consistently produce adequate space closure of up to 6 mm by progressively tipping teeth into spaces in small increments and can successfully straight dental arches by derotating teeth, especially when composite attachments are bonded (58–60).

On the other side, the PAR index revealed on the whole no significant differences between aligners and braces, with the exception of an almost significant difference in PAR reduction ($P = 0.06$; Table 2) and significant differences in the PAR components for upper anteriors and overbite ($P < 0.05$; Supplementary Table7) that favoured braces. This discrepancy between the results of the ABO-OGS and the PAR index can be explained by integral differences between components of the two tools. The PAR index was developed to assess in a systematic manner the outcome of orthodontic treatment in order to be incorporated in both quality assessment measures of orthodontic care and scientific research. It provides however a vague assessment of the occlusion and disregards aspects like tooth inclination, remaining spaces, and alignment of the posterior dental arch, which are important variables for board examination cases (32). It does not provide a detailed assessment of the tooth relationship within an ideal dental arch as the ABO-OGS does, which was developed in order to assess the fine details expected to be seen in a meticulously finished case in all three planes (first, second, and third order). Reported limitations of the PAR index (61) include among others a low weighting for overbite scores and high weighting for overjet scores (62). Indeed, post-treatment PAR scores do not correlate significantly with post-treatment ABO-OGS scores (63, 64). Subsequently, the PAR index has been widely used to also assess the baseline severity of a case. However, the PAR index to this end does not consider aspects like skeletal discrepancies/cephalometric values, developmental tooth anomalies, ectopic teeth, or soft tissues relationships and again does not correlate well with the ABO DI (63).

Overall and especially with regard to orthodontic treatment outcomes, it is apparently straightforward that the clinician's expertise might play a significant role not only with regard to the selection of the most appropriate treatment modality for each case, but is also closely linked to the administered quality of treatment outcomes, as performed by the operators/ clinicians. As such, efforts for future research should be directed not only towards high quality randomized trials that may mitigate bias stemming from extra-operator predictors such as patients' clinical characteristics or levels of response/compliance, but also towards studies streamlining the effect of different levels of clinician's expertise to the retrieved treatment outcomes.

Data synthesis on treatment duration with aligners or braces was not possible to be robustly conducted, since a very heterogeneous image emerged (Figure 4). There exist both studies that favour one or the other appliance with significant differences, as well as studies that show no significant difference (Figure 4). Therefore, it is logical to assume that appliance choice alone is not sufficient to considerably dictate treatment duration and other factors need to be taken carefully into account in future studies like baseline severity, extractions, number of aligners/refinements, and standard of care to which patients are treated.

As far as adverse effects of treatment are concerned, a single identified study on EARR (57) reported that significantly smaller percentage of the incisors' root was resorbed during treatment compared to braces (MD: −1.8%; $P < 0.001$; Table 4). It must also here be stressed out that evaluation of EARR during treatment is complicated, since many risk factors come into play including the patient's genetic predisposition towards EARR (65), the chosen mechanotherapy (66), the duration of treatment (67), and the actual amount of tooth movement (and especially apical movement) (65). A carefully conducted retrospective non-randomized study taking confounders like baseline severity through ABO DI, genetic polymorphisms, and absolute apical displacement into account concluded that treatment with orthodontic aligners results in similar amounts of EARR compared to fixed appliances. Therefore, it might be prudent to check if any significant differences in EARR reported in the literature are not rather due to teeth being actually moved less around with aligners.

Furthermore, no significant difference in the development of gingival recessions 2 years after treatment with aligners or fixed appliances was seen in another single study ($P = 0.86$) (53). It might be expected that choice of appliance alone might not directly influence the development of gingival recession. Even if appliance choice was associated with increased anterior anchorage loss/incisor proclination (which was not seen), this would not necessarily translate to increased risk of gingival recession (68, 69). Although orthodontic treatment on average increases the risk for gingival recessions (70), its precise etiology is multifactorial with risk factors including periodontal disease, mechanical trauma, patient age, smoking, and induction of bone dehiscences by positioning the teeth beyond the limits of the alveolar plate (69, 71).

Finally, limited evidence on the effect of appliance choice on loss of periodontal attachment was provided by a single identified study (51), which assessed orthodontic alignment of anterior teeth in adult patients with previous history of treated periodontal disease. After retrieving raw data from the author and matching the study's groups for baseline status, no differences between aligners and fixed appliances were seen for periodontal probing depth ($P = 1.00$) or alveolar bone levels ($P = 0.69$). On the other side, fixed appliances were significantly quicker repositioning the patients' migrated anterior teeth compared to aligners (3.9 versus 6.0 months; $P = 0.01$). It must be noted that although previous systematic reviews of mostly methodologically compromised studies have reported that aligners might be associated with facilitation of better oral hygiene than fixed appliances (17, 22, 54), a recent RCT (72) found no significant and consistent advantage in terms of plaque index, gingival index, or periodontal bleeding index between patients treated with aligners and fixed appliances. Therefore, fixed appliances can also be compatible with proper oral hygiene.

Strengths and limitations

This systematic review has several strengths, comprising an a priori registered protocol (15), a comprehensive literature search, the inclusion of randomized or matched non-randomized studies, the use of modern analytic methods (36), the application of the GRADE approach to assess the strength of provided recommendations (39), and the transparent provision of all data (73).

Some limitations also do exist in the present review. For one, methodological issues existed for all included studies that might influence conclusions, and this is especially the case for included retrospective non-randomized studies (11, 13). Selection bias may not be ruled out when non-randomized designs are used; however, in an attempt to reduce the risk for such a potential limitation due to dissimilarity of groups under comparison, we solely included studies with populations matched for baseline characteristics. Inclusion of non-randomized studies in meta-analysis is not considered prohibitory, provided robust bias appraisal has been performed, and recent guidance has been provided about how to appropriately incorporate such designs (40). Also, a heterogeneous response among studies was seen for many outcomes, which is to be expected due to the wide spectrum of malocclusions, appliances, and clinical settings included. This heterogeneity affected however mostly the magnitude and not the direction of the effects, except from the outcome of treatment duration, where no consistent effect of appliance choice could be seen. Furthermore, most meta-analyses were based predominantly on small trials, which might affect the precision of the estimates (74). Additionally, the small number of trials that were ultimately included in the meta-analyses and their incomplete reporting of results and potential confounders like level of case severity, oral hygiene, compliance, use of bonded attachments, number of aligners, rate of refinement need, or amount of interproximal enamel reduction precluded the conduct of many analyses for subgroups and meta-regressions that might enable identification of patient subgroups for which aligners might be an equal or even more appropriate treatment alternative compared to fixed appliances.

Conclusions

According to currently existing clinical evidence from randomized trials and matched non-randomized studies on mostly adult patients with mild to severe malocclusions treated with or without extractions, it seems that orthodontic treatment with aligners is associated with worse treatment outcomes compared to fixed appliances. Treatment duration does not seem to be defined by appliance alone and patient or treatment-related factors might come into play. For adverse outcomes such as EARR, proclination of lower incisors and development of gingival recessions, limited data exists and further individual well-conducted trials will be useful in formulating robust conclusions.

Supplementary material

Supplementary materials are available at *European Journal of Orthodontics* online.

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Conflicts of interest

None to declare.

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PUBLICATION
IV

Effect of cleansers on the composition and mechanical properties of orthodontic aligners in vitro

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Effect of cleansers on the composition and mechanical properties of orthodontic aligners in vitro

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Abstract

Background: The aim of the study was to investigate the effect of three aligner cleaners on the composition and mechanical properties of two types of orthodontic aligners.

Materials and methods: The cleaners tested were two alkaline peroxide solutions (Retainer Brite—RB; Retainer Cleaner—RC) and one peroxide-free (Steraligner—ST) and the aligners Clear Aligner (C, polyester) and Invisalign (I, polyester–urethane). The aligners were immersed in the cleaner solutions as instructed every day (15 min for RB, RC; 5 min for ST) for a two-week period. The acidity of the solutions was tested with a pH meter. The changes in the chemical composition of the aligners were studied by attenuated total-reflection Fourier transform infrared spectrometry (ATR-FTIR), while Instrumented Indentation Testing (IIT) was used for assessment of changes in Martens Hardness (HM), modulus (E_{IT}), elastic index (n_{IT}) and relaxation (R_{IT}).

Results: RB and RC were weakly acidic (pH = 6.3), whereas ST was mildly acidic (pH = 4.8). The ATR-FTIR analysis demonstrated evidence of acidic hydrolysis of C in ST and I in RB. The IIT-derived properties of I were not affected by the cleaners. However, for C a significant change was found in HM (all cleaners), n_{IT} (all cleaners) and R_{IT} (RB, ST). Although the chemical changes support a hydrolytic material deterioration, the results of mechanical properties may interfere with the material residual stresses during fabrication.

Conclusions: Caution should be exerted in the selection of aligner cleaners. The mild acidic cleanser was more aggressive to the polyester, whereas an alkaline peroxide to the polyester–urethane aligner.

Keywords: Cleansers, Aligners, Mechanical properties, Chemical alterations

Introduction

Aligner system technology provides an orthodontic treatment modality for patients regarding aesthetics highly [1, 2]. The sequential positioners are usually fabricated out of poly(ester–urethane) (PU) or polyethylene terephthalate glycol (PET-G) thermoplastic materials [3] which are translucent and difficult to detect with naked eye. Every aligner becomes deformed upon placement exerting light forces to the teeth. Each removable appliance remains intraorally for two weeks usually, until being replaced by the following new one, inducing tooth movement in an incremental fashion. During this short period, the stability of their properties is of major importance for clinical effectiveness [4].

A major issue with these devices is that the stagnation of salivary flow make their internal surfaces prone to plaque accumulation [5, 6] and staining [7–9]. Calculus formation, although not very common, cannot be excluded, as well. Thus, it becomes imperative for the patients to retain oral hygiene [10] at an appropriate

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level and remove any debris left in the aligner surfaces. For that purpose, chemical cleaners have been developed requiring no patient dexterity unlike to the toothbrush/toothpaste or soap combination alternatives. These are mild sanitization solutions of various acidity containing sodium bicarbonate, acids, sulfates, chelators and a variety of salts. The cleaners are capable of efficiently removing bacteria biofilms, restoring the original translucency of the appliances and offering a pleasant odor when immersed daily for a few minutes [5, 6, 11–13]. However, the reactivity of the cleaners has raised questions on possible chemical modifications of the aligners and consequently on their mechanical properties, which may adversely affect the treatment outcome. In the relevant literature, the information available for such side effects regarding this interaction is limited and involves mainly thermoplastic retainers [11–15] used to stabilize the orthodontic treatment outcome. In particular, changes were observed in the flexural modulus of chemically cleaned retainers made of copolyester [12], whereas those of polypropylene/ethylene copolymer [13] or polyurethane [14] did not present significant deviations. For aligners, the effect of cleaners on the time-dependent mechanical properties of the devices, which are crucial for the stress-transfer characteristics of the light continuous forces to the teeth, has not been addressed so far.

The aim of the present study was to evaluate the changes in the mechanical properties and surface chemistry of aligners treated with cleaning solutions of different composition. The null hypothesis was that the cleansers have a negligible effect on the properties tested.

Materials and methods

Materials

The aligners and the cleaning agents tested are presented in Table 1. Forty unused upper aligners of Clear Aligners (C) and Invisalign (I) aligners were obtained from an orthodontic practice and classified into four groups of ten specimens each per material. The cleansing solutions of RB ad RC were prepared by dissolving each tablet in 150 ml of tap water, whereas for ST 15 ml of the liquid was mixed with 135ml of tap water.

Aligners designated for Retain Brite (RB) and Retain Cleaner (RC) treatment groups were immersed in individual caps with the cleaning agents for 15 min, whereas a 5-min immersion period was used for the Steraligner (ST) group, according to the manufacturer's instructions. After each cleansing cycle, the aligners were rinsed thoroughly with tap water and then stored in dry conditions. This procedure was repeated 14 times, once per day for a two-week period, corresponding to a daily cleaning during the instructed in-service function of each appliance. Aligners non-immersed in the cleaning solutions were used as control (CO).

pH measurements

The pH of 150 ml freshly made cleaning solutions was measured by a calibrated pH meter (P 903, Consort NV, Turnhout, Belgium) employing a standard liquid probe. Measurements were performed two minutes after mixing in triplicate and the values were averaged.

Mechanical properties (IIT)

Ten upper first molars from different appliances of each testing group (RB, RC, ST, CO) per aligner type (C, I) were sectioned. The specimens were embedded in self-curing acrylic resin (Verso Cit-2, Struers, Ballerup,

Table 1 The aligner materials and the cleaning agents used in the study

Product/code	Composition*	Manufacturer
Aligners		
CA Clear Aligner/C	Polyethylene terephthalate glycol	Scheu-Dental GmbH, Iserlohn, Germany
Invisalign/I	Polyester–urethane	Align Technology, San Jose, CA, USA
Cleaning agents		
Retainer Brite/RB	Potassium peroxymonosulfate, Sodium perborate monohydrate, Sodium bicarbonate, Sodium sulfate, Sodium carbonate, Pentasodium triphosphate, Corn syrup solids, Sodium lauryl sulfoacetate, PEG-180, Flavor, Magnesium stearate, Tetrasodium EDTA, Citric acid, FD&C Blue #1, FD&C Blue #2	Dentsply Sirona, Sarasota, FL, USA
Retainer Cleaner/RC	Potassium peroxymonosulfate, Sodium percarbonate, PEG-150, Peppermint oil, Indigo, Sodium benzonate, Sodium bicarbonate, Tetrasodium EDTA, Sodium lauryl sulfate	Fancymay, Greenland, (Amazon Associate)
Steraligner/ST	Surfactant, Polyrsorbate 20, Sodium pyrophosphate, Tetrapotassium salt (undefined), Essential oil complex, Sodium gluconate, 2-propanol, Disodium EDTA, Sodium benzonate, Sodium bicarbonate, FD&C Blue #1	TJA Health LLC, Joliet, IL, USA

* According to the manufacturers' information

Denmark), with their occlusal surfaces parallel to the horizontal plane. The samples were ground up to 4000 grit-size SiC papers under water cooling, and polished with a water-based diamond suspension (Nap R1 DiaPro, Struers) in a grinding/polishing machine (Dap-V, Struers). Then, the specimens were subjected to Instrumented Indentation Testing (IIT), employing a universal hardness testing machine (ZHU0.2/Z2.5, Zwick Roell, Ulm, Germany) with a Vickers indenter for determination of the following mechanical properties: the Martens Hardness (HM), indentation modulus (E_{IT}), elastic index (n_{IT}) which is indicative for the brittleness of the material, and the indentation relaxation (R_{IT}). Two different loading regimes were applied. The HM, E_{IT} and n_{IT} were acquired from force–indentation depth curves applying a maximum load of 2.9 N for 2 s contact time. The R_{IT} (monitoring the load level, while maintaining a constant contact area between the indenter and the material) was measured employing a tetragonal force pulse where a constant indentation depth was applied for 60 s and the R_{IT} was measured by recording the force decrease between the start and the end of the constant indentation depth period. All mechanical properties were measured according to the equations provided by the international standard ISO14577-1, 2002 [16].

Surface chemical composition (ATR-FTIR)

Another series of specimens was prepared by sectioning as above. Intact occlusal specimen surfaces were analyzed by Attenuated Total Reflectance Fourier Transform Infrared Spectrometry (ATR-FTIR), employing a spectrometer (Spectrum GX, PerkinElmer, Buckinghamshire, Bacon, UK) equipped with an ATR accessory (Golden Gate, Specac, Orpington, Kent, UK) with a diamond type III crystal (2 × 2 mm) and a sapphire anvil. Spectra were acquired after under the following conditions: 4000–650 cm^{-1} wavenumber range, 4 cm^{-1} resolution, 20 scans co-addition, 2 μm depth of analysis at 1000 cm^{-1}. The spectra of treated specimens were compared with the controls to identify changes in peak positions indicating the presence of new chemical groups. Furthermore, to verify the H-bonding status of the polyester backbone, the 1800–1650 cm^{-1} wavenumber range of all spectra was subjected to curve-fitting analysis (Gaussian area mode) employing PeakFit v.4.12 software (Seasolve, Framingham, MA, USA).

Statistical analysis

The results of pH and mechanical properties were initially tested for normality (Shapiro–Wilk) and homoscedasticity (Brown–Forsyth) tests. For normally distributed data, comparisons were carried out by one-way ANOVA, whereas for data failed to pass normality tests, the nonparametric one-way ANOVA on Ranks (Kruskal–Wallis) test was used. In all cases, Tukey post hoc multiple comparison tests were used to allocate differences among groups. The level of statistical significance for all tests was set at $a = 0.05$. Statistical analysis was carried out employing SigmaPlot v 14 software (Systat Software Inc, San Jose, CA, USA).

Results

pH measurements

The RB and RC cleansers showed a similar pH value (6.31 ± 0.02), whereas the ST cleanser showed a significantly lower pH value (4.83 ± 0.04).

Mechanical properties (IIT)

Figure 1 demonstrates representative force–indentation depth (a, c) and force–time curves (b, d) for the aligners (C, I) per cleaner group (RB, RC, ST) and the control (CO).

For Clear Aligner, a shifting of the peak of the load–indentation graph was found toward higher indentation values after all cleaner treatments in comparison with the control (a), which implies a softening effect. Moreover, two of the cleaner treatments (RB, ST) demonstrated lower force decay overtime from RC and the control (b). The results are summarized in Table 2. All the cleaners comprised a statistically homogeneous group with significantly lower HM, n_{IT} values from the control. Insignificant differences were found between the groups in E_{IT}, whereas the R_{IT} measurements revealed significantly reduced values of RB, ST groups from RC and the control (CO).

For Invisalign, the loading and unloading curves were identical (a, b) indicating insignificant differences between the cleaner groups tested and the control, as is verified from the numerical data given in Table 3.

Surface chemical composition (ATR-FTIR)

Representative ATR-FTIR spectra of the aligners before and after cleaning treatments are illustrated in Figs. 2, 3 and 4.

For Clear Aligner (Fig. 2), the peak assignments are as follows (cm^{-1}): 2926 and 2854 (C–H stretching) [not shown in the expanded spectra of the figure]; 1712 (C=O stretching); 1577, 1604 (aromatic C–C stretching); 1450, 1408, 1369 (C–H bending); 1257, 1240 (C=O stretching), 1173 (C–H bending); 1113, 1093 (C–O– stretching); 1016 (C–C ring bending), 956 (C–H stretching of the cyclohexylene ring); 875, 723 (aromatic C–H bending) [17–19]. The cleaning procedures showed similar spectra, except for ST, which demonstrated a small peak at 1670 cm^{-1} assigned to acid groups [20]. The curve-fit analysis of the ester peak of Clear Aligner (Fig. 3 and

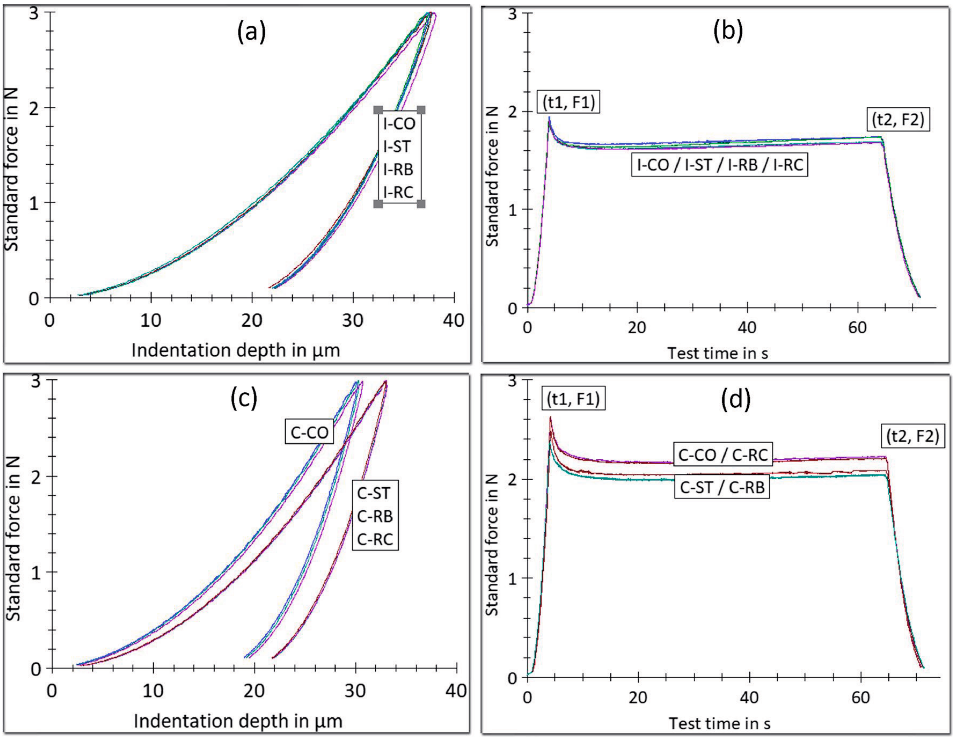

Fig. 1 Representative force–indentation depth (**a**, **c**) and force–time curves (**b**, **d**) for Clear Aligner (C) and Invisalign (I) appliances after immersion in Retainer Brite (RB), Retainer Cleaner (RC) and Steraligner (ST) solutions vs the controls (CO)

Table 2 The results of the IIT-derived mechanical properties for Clear Aligner (C)

Group	HM (N/mm^2)	E_{IT} (MPa)	n_{IT} (%)	R_{IT} (%)
C–CO	112 (6)[a]	2699 [2414 2991]	40.6 (0.7)[a]	8.4 [7.9 12.8][a]
C-RB	106 (3)[b]	2469 [2409 3034]	39.0 (0.6)[b]	15.1 [14.1 15.6][b]
C-RC	108 (1)[b]	2529 [2352 3041]	39.1 (0.5)[b]	9.0 [8.4 9.2][a]
C-ST	107 (3)[b]	2466 [2376 2643]	38.6 (0.6)[b]	12.1 [8.7 13.3][b]

Mean values and standard deviations (in parentheses) or median and 25% and 75% percentiles (in brackets). Same superscript letters show groups without statistical differences per property ($p > 0.05$)

Table 3 The results of the IIT-derived mechanical properties for Invisalign (I)

Group	HM (N/mm^2)	E_{IT} (MPa)	n_{IT} (%)	R_{IT} (%)
I-CO	80 (4)	1615 (148)	44.7 [44.2 45.9]	9.3 [6.5 11.4]
I-RB	80 (5)	1605 (141)	43.6 [42.4 44.6]	9.2 [6.9 12.3]
I-RC	79 (4)	1558 (197)	46.0 [45.0 46.6]	8.5 [7.6 9.2]
I-ST	83 (5)	1709 (148)	45.6 [45.2 46.4]	9.6 [5.4 13.8]

Mean values and standard deviations (in parentheses) or median and 25 and 75% percentiles (in brackets). No statistically significant differences were found between the immersion groups and the control for the properties tested ($p > 0.05$)

Table 4) showed two major peaks at 1727 cm^{-1} (free C=O groups) and 1712 cm^{-1} (H–bonded C=O groups) comprising 90–93% of the total C=O peak area ($tA_{C=O}$) at a ratio of 0.4–0.5 (free to H–bonded, based on mean values) for RB, RC and CO, ST, respectively. All specimens showed minor peaks at 1740 cm^{-1} (2–4% of $tA_{C=O}$) and 1693 cm^{-1} (5–6% of $tA_{C=O}$) possibly assigned to oxidation byproducts.

The control group demonstrated approximately twice the area of the 1740 cm^{-1} peak in comparison with the treated groups (4 vs 2 for ST and 2.1 for RB, RC), whereas the differences in the 1690 cm^{-1} peak area were smaller (5.7 vs 4.1 for ST and 4.8 for RB, RC). The ST group demonstrated additionally two low wavenumber peaks (1677 and 1644 cm^{-1}, 5.9% in sum of $tA_{C=O}$) attributed to acid formation [20].

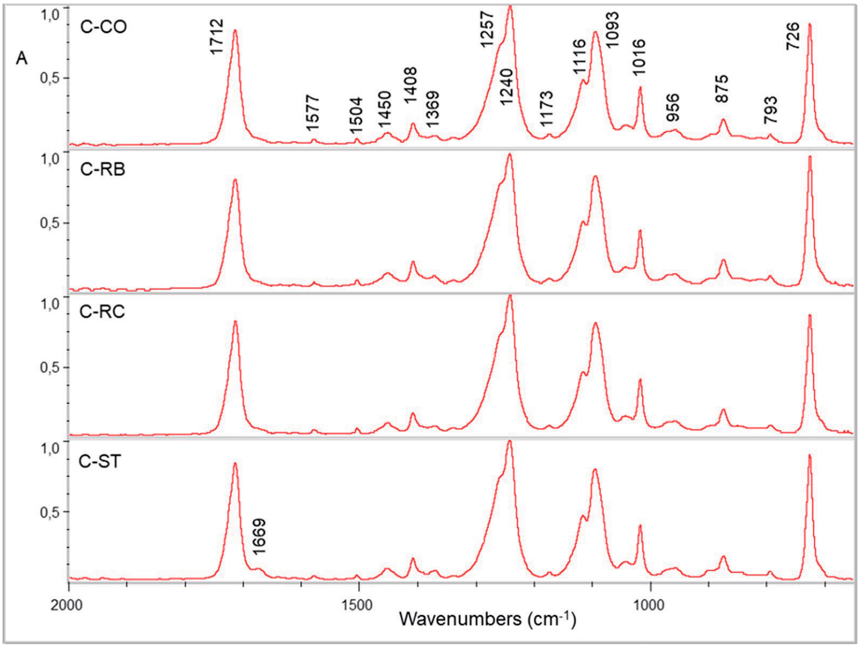

Fig. 2 ATR-FTIR spectra of Clear Aligner (C) before (CO) and after treatments with Retainer Brite (RB), Retainer Cleaner (RC) and Steraligner (ST) cleaners. An additional peak appeared at 1669 cm^{-1} after ST cleaner (expanded 2000–650 cm^{-1} range, absorbance scale)

For Invisalign (Fig. 4), the peak assignments are as follows (cm^{-1}): 3330–3270 (N–H stretching); 2927–2919 and 2850 (C–H stretching) [not shown in the expanded spectra of the figure]; 1726–1699 (C=O stretching); 1609 and 1595 (aromatic C–C stretching); 1526 (C–N and N–H bending); 1477, 1412, 1365 (C–H bending); 1310 (C=O vibrations), 1252 (C–N and C–O stretching); 1220, 1105, 1064 and 1017 (C–O–C stretching) 816 and 770 (aromatic C–H bending) [17, 21]. No differences were found after the cleaning treatments and the controls.

The curve-fit analysis of the ester peak of Invisalign (Fig. 5 and Table 5) resolved four peak components assigned to polyurethane (hard polymer segment) or polycarbonate (soft polymer segment) of poly(ester–urethane) polymers at 1732 cm^{-1} (free C=O groups of urethane and carbonate components), 1714 cm^{-1} (H–bonded C=O groups of carbonate component), 1699 cm^{-1} (H–bonded C=O groups of amorphous urethane component) and 1683 cm^{-1} (H–bonded C=O groups of low-ordered urethane component) [22]. The free C=O accounted for 16.7–18.2% of the $tA_{C=O}$ (mean values) and were not affected by the treatments. The same applied for the H–bonded C=O groups of the carbonate segment (21.7–23.8%). However, for the amorphous urethane H–bonded C=O groups, a reduction in the peak area was found after RB treatment (39.8%) in comparison with the control (50.5%) and the other treatments (50.3% for RC and 44.3% for ST). This difference was in favor of the low-ordered urethane H–bonded C=O groups, which increased after RB treatment (16.3%) in comparison with the control (9.8%), RC (11%) and ST (8.6%).

Discussion

The orthodontic force delivered by aligners depends on material thickness, hardness, elastic modulus and amount of activation [1]. To predictably move teeth, it is important that the mechanical properties of the aligners to be stable during the in-service period [2]. However, during usage the aligners are not only exposed to the oral environment, but should be treated with disinfecting and cleaning solution for hygienic purposes [3–7] The results of the present study showed that some cleaners may affect the mechanical properties or/and the surface chemistry of aligner materials fabricated by polyethylene terephthalate glycol (PET-G) or poly(ester–urethane). Consequently, the null hypothesis should be partially rejected.

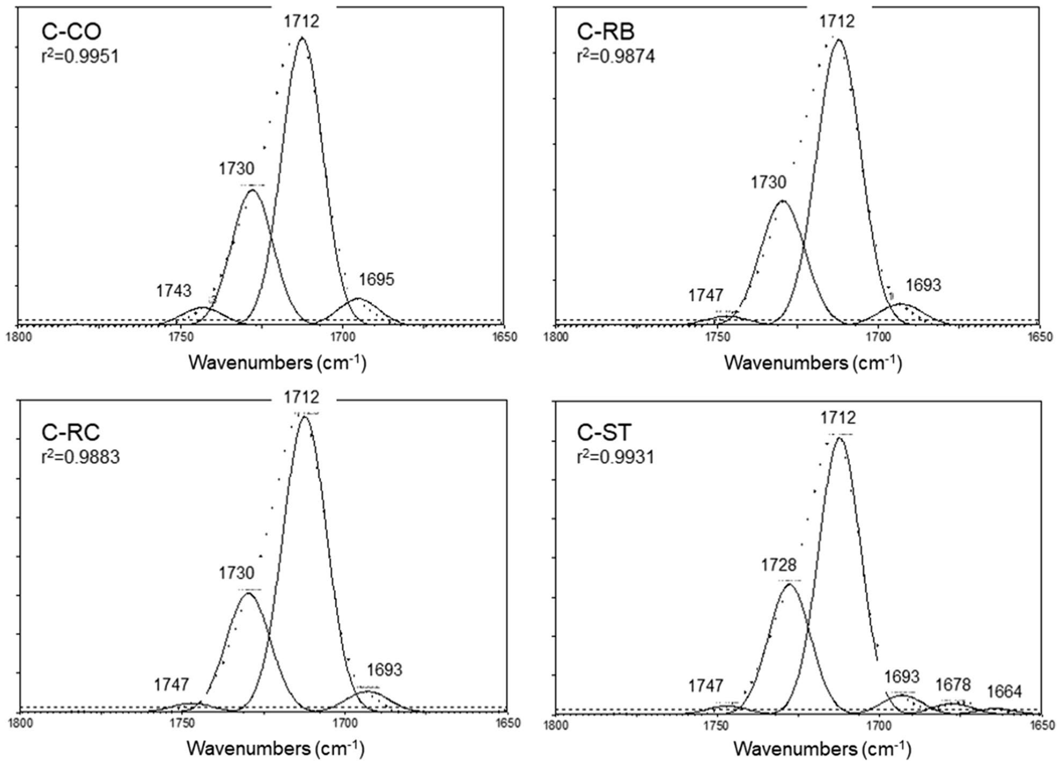

Fig. 3 Gaussian curve-fitting of the ester peak of Clear Aligner before (CO) and after treatments with Retainer Brite (RB), Retainer Cleaner (RC) and Steraligner (ST) cleaners. The additional peak after ST cleaner at 1669 cm^{-1} of Fig. 2 is analyzed in two peaks at 1678 cm^{-1} and 1664 indicating formation of acid derivatives (1800–1650 cm^{-1} range, absorbance scale, dotted lines: original spectra, r^2: coefficient of determination for the goodness of curve-fit)

The cleaners tested have been specifically designed for orthodontic aligners, although the quantitative composition of some (RB, RC) resembles that of conventional denture-base cleaners [23]. RB and RC cleaners are mainly composed of sodium perborate or sodium percarbonate, which in water solutions decompose to borates and hydrogen peroxide or hydrogen peroxide with sodium and carbonate ions. The hydrogen peroxide further decomposes to active oxygen and water, whereas the carbonates to carbon dioxide and water [24]. The cleansers contain surfactants, flavoring agents and pigments. It has been documented that the cleaners of this category (commonly referred to as alkaline peroxides) reduce the hardness and flexural strength and increase the roughness of polymethyl methacrylate denture-base materials through hydrolytic oxidation and network plasticization (extraction of residual methyl methacrylate monomer, cross-linkers, oxidation byproducts, etc.) [25, 26]. For ST, the composition given does not define any source of active oxygen as in the other two cleaners, the only difference being the lower pH. All the cleaners contain EDTA chelators. EDTA is known to inhibit biofilm formation, especially the tetrasodium salt [27], whereas the disodium demonstrates increased solubility in water and a faster chelation effect [28]. Also, pyrophosphates and polyphosphates are used as inhibitors of Ca and Mg precipitation on the appliances [29, 30].

In the present study, none of the mechanical properties of the Invisalign aligners showed significant difference after immersion in any of the three cleaning solutions in comparison with the control group. This implies that the poly(ester–urethane) structure of Invisalign was stable to the degradative effects of the cleaners tested. However, for Clear Aligner, a significant reduction in Martens Hardness and elastic index was manifested, which indicates that these aligners became softer and more brittle, irrespectively of the active ingredients and the pH of the cleaners used. A

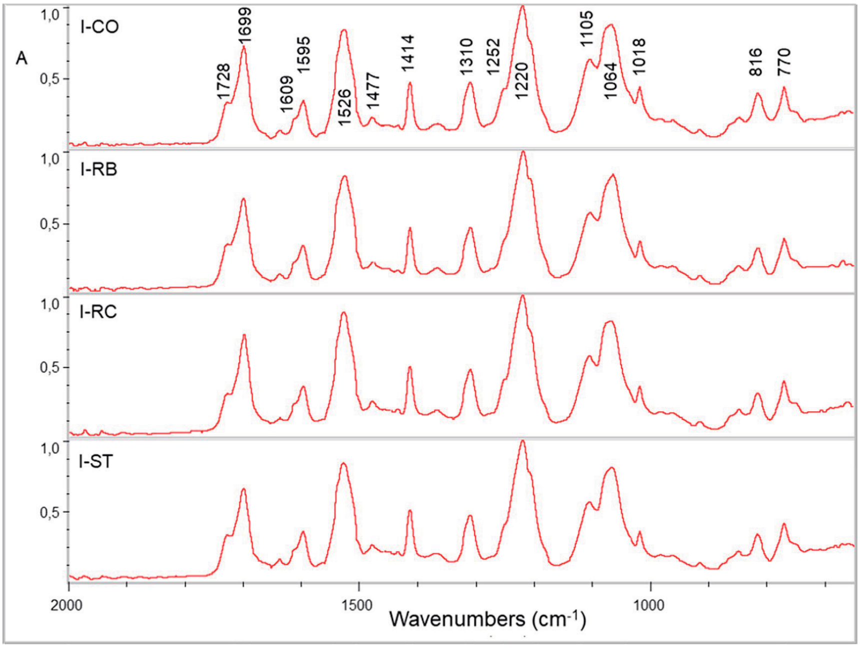

Fig. 4 ATR-FTIR spectra of Invisalign (I) before (CO) and after treatments with Retainer Brite (RB), Retainer Cleaner (RC) and Steraligner (ST) cleaners. Spectra are identical (expanded 2000–650 cm^{-1} range, absorbance scale)

Table 4 The results of the curve-fitting analysis of the ester peak for Clear Aligner (C)

Group	Peak area (%)					
	1743 cm^{-1}	1727 cm^{-1}	1712 cm^{-1}	1693 cm^{-1}	1677 cm^{-1}	1664 cm^{-1}
C–CO	3.9	29.1	61.3	5.7	–	–
C-RB	2.1	28.5	64.6	4.8	–	–
C-RC	2.1	26.9	66.2	4.8	–	–
C-ST	1.9	27.7	60.4	4.1	3.4	2.5

1727 cm^{-1}: Free C=O groups; 1712 cm^{-1}: H–bonded C=O groups; 1743, 1693 cm^{-1}: Oxidation byproducts; 1677, 1664 cm^{-1}: Acid impurities

possible explanation is an increased hydrolytic instability of the esterified hydrophilic polyglycol segments of the amorphous PET-G. An interesting finding of the study was the different effects of RB and RC cleaners in R_{IT}, which is associated with the behavior of the aligner materials under creep. RC with the same pH with RB was less aggressive to Clear Aligner, matching the effect of the control group, while RB demonstrated significantly higher R_{IT} values from RC, being similar with the acidic ST. This may suggest that several compositional factors, other than the pH, may induce the hydrolytic degradation. In industrial applications, sodium percarbonate is considered more reactive than sodium perborate, with the latter requiring additional alkalinity (usually mediated by solutions of 1% NaOH) for an effective bleaching effect [31]. It is not known if a similar mechanism is implemented in RB, which would explain the difference. Furthermore, a parameter which may affect the mechanical properties of the aligners is the undefined role of residual stresses developed during the manufacturing process [32]. Successive immersion may provide an extent of relaxation with a subsequent effect on the mechanical properties measured [32]. However, the extent and orientation of residual stresses

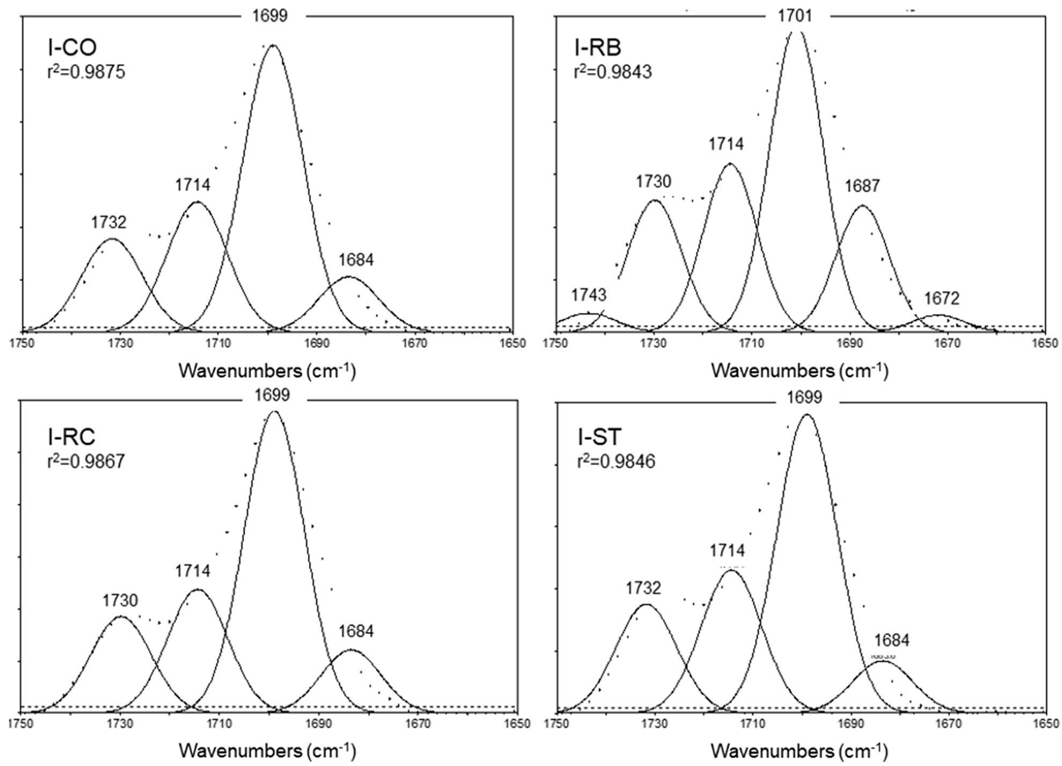

Fig. 5 Gaussian curve-fitting of the ester peak of Invisalign (I) before (CO) and after treatments with Retainer Brite (RB), Retainer Cleaner (RC) and Steraligner (ST) cleaners. After RB treatment, two additional peaks appeared (1743 cm^{-1}, 1672 cm^{-1}) and the intensity of the peak at 1687 cm^{-1} was increased indicating changes in the H–bonding status of the ester groups (1750–1650 cm^{-1} range, absorbance scale, dotted lines: original spectra, r^2: coefficient of determination for the goodness of curve-fit)

Table 5 The results of the curve-fitting analysis of the ester peak for Invisalign (I)

Group	Peak area (%)					
	1743 cm^{-1}	1732 cm^{-1}	1714 cm^{-1}	1699 cm^{-1}	1684 cm^{-1}	1672 cm^{-1}
I-CO	–	16.7	23	50.5	9.8	–
I-RB	2.5	17.2	21.9	39.8	16.3	2.3
I-RC	–	17	21.7	50.3	11	–
I-ST	–	18.2	23.8	44.3	8.6	–

1732 cm^{-1}: Free C=O groups of urethane and carbonate; 1714 cm^{-1}: H–bonded C=O groups of urethane and carbonate; 1699 cm^{-1}: H–bonded C=O groups of amorphous urethane segments; 1684 cm^{-1}: H–bonded groups of low-ordered urethane segments; 1743, 1672 cm^{-1}: Acid impurities

of orthodontic retainers still remain unknown. This may be an interesting topic for further research.

To characterize the chemical changes induced on the aligner surfaces, an ATR-FTIR analysis was used. Although the sampling depth of the method is limited to the uppermost 2 μm zone (vs bulk characterization of ground/polished specimens by IIT), it may provide important information on the degradation mechanisms involved. Comparison of the spectra at the fingerprint range (2000–650 cm^{-1}) showed a difference only in Clear Aligner treated with ST, where a peak appeared at 1699 cm^{-1} attributed to acid production via oxidation of the PET structure [20]. A more detailed analysis by curve-fitting of the ester peak components demonstrated the presence of free and H–bonded C=O groups at a ratio of 0.4 for RB, RC and 0.5 for CO and ST. The small reduction observed after treatment with the alkaline peroxides (RB, RC) may suggest degradation of a small fraction of free-ester groups. The highest and lowest wavenumber weak peaks (1743, 1693 cm^{-1}) found in all groups indicate that oxidized impurities existed in the control and where reduced after treatments, mainly at the highest wavenumber. The two additional peaks resolved at 1677 and 1644 cm^{-1} suggest that the acid produced may appear in more than one forms (terephthalic, glycolic, etc.). Considering the depth of the ATR and IIT methods, it may be concluded that the chemical changes may exceed up to the depth of the IIT method, affecting the mechanical properties accordingly. Curve-fitting of the ester peak components revealed some interesting information for Invisalign, the mechanical properties of which were not affected by any of the cleaners, as documented by the fingerprint range spectra. After RB treatment, weak highest (1740 cm^{-1}) and lowest (1672 cm^{-1}) wavenumber peaks appeared indicating oxidative effects, while the peak at 1687 cm^{-1} assigned to the low-ordered crystallinity of the urethane segment was increased at the expense of the corresponding amorphous (1699 cm^{-1}). This may indicate an onset of the development of a more brittle structure, possibly associated with aging. The fact that this phenomenon was observed only after treatment with one alkaline peroxide (RB), suggests that the poly(ester–urethane) structure is more sensitive to this type of cleaners and that RB is a stronger alkaline peroxide than RC. Although the chemical changes of Invisalign were not associated with the mechanical response, they clearly demonstrate the capacity of ATR-FTIR spectrometry in identifying early degradative changes in the surface chemistry of the aligners.

The results of the present study should be carefully interpreted since the aligners were not subjected to intraoral conditions, to reliably assess the extent of the cleaner-induced degradation in the performance of intraorally exposed analogues. Such changes, though, documented in simple immersion tests may contribute to the earlier deterioration of the aligner properties, possibly affecting the in-service life of the devices. Further studies, considering in vivo functional loading as a testing factor may enlighten the role of the cleansers to the properties of the aligners and facilitate defining the onset of the mechanical deterioration of these thermoformed materials.

Conclusion

The mechanical properties of the Invisalign aligners devices did not change after immersion in the cleaning solutions (two alkaline peroxides and one acidic), whereas Clear Aligner devices showed evidence of softening and brittleness (all solutions) and increased relaxation in two solutions (alkaline peroxide and acidic). However, these changes may be implicated with residual stresses.

The surface chemical analysis revealed acid formation in Clear Aligner after the acidic treatment, whereas the H–boned status analysis of Clear Aligner ester groups manifested a small reduction of the free-ester groups after alkaline peroxide treatments. Changes in Invisalign surface chemistry were registered only for one alkaline cleaner by the H–bonding status analysis of the ester groups, suggesting early signs of degradation.

Based on these findings, the cleaners tested should be used with caution in PET-G aligners, while some alkaline peroxide solutions should be avoided for cleaning poly(ester–urethane) aligners.

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Author contributions
TE was involved in the conception and design of the work; AI, VE, GP and SZ helped in experimental configuration, materials, specimen preparation; AI, VE, SZ, TP and TE contributed to acquisition, analysis, and interpretation of data; all were involved in drafting and editing. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate
This is an in vitro study and ethic approval does not apply in this case.

Consent for publication
Not applicable.

Competing interests
None from the authors have any competing or financial interest.

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Publisher's Note

Surface alterations of resin composite attachments by induced orthodontic aligners: An in-vitro study

Iliadi A, Koletsi D, Schaetzle M, Eliades G (manuscript-part of the European Orthodontic Research Grant 2019).

Introduction

Over the past decades a significant increase in the utilization of sequential clear aligners in orthodontic treatment has occurred[1]. A growing interest has been reported for such methods especially among adult patients which can be attributed, in part, to the extensive marketing efforts undertaken by manufacturers[2]. During the course of orthodontic treatment with aligners, each aligner is commonly used for either one or two weeks and thereafter it is replaced by its sequential successor. The initial force magnitude depends on the material mechanical properties. With time, the material structural instability in combination with residual stress relaxation due to intraoral ageing results in force decay[3]. Moreover, intra-oral aging has a detrimental effect on surface roughness and mechanical properties of aligner type appliances, although it has been shown that this effect is restricted to the first week of clinical use[4].

Resin composite attachments are based on conventional particle reinforced dimethacrylate resin technology, with glass particles embedded in BisGMA or analogue (BisEMA, BisPMA, BisGMA-isocyanate adducts etc) monomer resin matrices with non-aromatic resin diluents (TEGDMA, UEDMA, HDDMA etc). These attachments are bonded to the tooth surface after implementing acid-etching, while dental adhesives used are based on similar monomers with the addition of phosphate/ carboxylic functionalized monomers, to mediate chemical adhesion in addition to micromechanical retention. Increased abrasion of the aligner surface in contact with the attachment evidently occurs, which is further accentuated by the removal and re-seating of the appliance, as a common procedure of aligner treatment. In addition, abrasive wear of the composite attachments is anticipated, which is associated with changes in surface morphologic characteristics, promoting biofilm retention and surface plasticization. In this context, Barreda et al.[5] examined the surface wear of resin composites with different filler loading and hardness for aligner attachments and detected no significant shape changes, but certain surface changes (i.e., cracks or fractures).

Related concerns on the safety of these monomers when released in the oral environment, have raised awareness regarding the determination and evaluation of BPA or other endocrine disruptor levels during orthodontic treatment with aligners. Such an assessment is considered of high priority for the following reasons: a) an increasing amount of patients tend to prefer orthodontic treatment with aligners over conventional brackets, b) treatment with aligners tends to become more popular among young patients, c) composite attachments are placed in the majority of cases treated with aligners and d) the total surface area of the attachments exposed to the environment is much greater than in conventional restorative applications and e) the attachments are mainly subjected to complex off-axis shear and bending forces. All these increase the extent of environmental interferences immediately after curing and establish operation of the attachments under a more stressful environment.

The aim of this study was to assess the changes in the morphology, roughness and composition of composite surfaces in contact with the aligners. The null hypothesis was that there are no differences in the properties tested in the morphology, roughness and composition between plain aligners and aligners with composite attachments and across time points.

Materials and methods

Experimental design and material

Zirconia CAD/CAM full arch frames (n=20) and corresponding thermoformed polyethylene terepthalate glycol (PET-G) aligners (Clear Aligners, Scheu-Dental, Iserlohn, Germany) with standardized spaces for the attachments (rectangular and ellipsoid). were manufactured. On each frame eight resin attachments were bonded on the buccal surfaces of central and lateral incisors, canines and first premolars. The attachments were bonded as follows: The zirconia frame surfaces were grit-blasted with 50 μm alumina employing an intraoral sandblasting device (Microetcher IIA, Danville Materials) operated for 5 s at 2.3 bar air pressure (0.23 MPa, 0.47 L/s flow rate), 5 mm distance and 90^{o} angle. The grit-blasted surfaces were then treated with a universal primer (G-Multi Primer, GC Europe NV, Leuven, Belgium) according to the manufacturer's instructions. Half of the attachment templates were filled with a sculptable universal composite restorative material (Group I, Tetric Evo Ceram, A2 shade, Ivoclar Vivadent, Shaan, Liechtenstein) whereas for the rest a low shrinkage universal flowable resin composite (Group II, Tetric Power Flow, A2 shade, Ivoclar Vivadent) was employed. Attachment templates were then pressed against the sandblasted zirconia frames and light-cured for 20 s (each attachment) with a LED curing unit (Bluephase G20i, Ivoclar Vivadent) emitting 1600 mW/cm^2 intensity in standard mode. After excess removal, the frames with the aligners were immersed in 50 mL of distilled water and stored in sealed vials at $37^{o}C$ under dark conditions. Eight aligners of each group were removed and re-seated to the zirconia frames 4 times per day for a 7-day immersion period, whereas the rest remained intact. After the testing period, the aligners were removed and the corresponding attachment surfaces being in contact with the aligner, were studied for morphological features, roughness and composition.

Morphological features

The attachments were examined under a stereomicroscope (M80, Leica) at 7.5 or 25× magnification under reflected light.

Roughness

All the bonded composite attachments were examined by an optical profiler (Wyko NT1100, Veeco, Tuscon, AZ, USA) employing a Mirau lens at 10× magnificaton (462.2 × 607.5 μm^2 analysis area), vertical scanning mode, 2% modulation and tilt correction. The 3D-roughness parameters determined were the Sa, Sq, Sz (amplitude), Sdr, Sds, Ssc (hybrid), and Sc, Sv (functional). Sa is the arithmetic average of the absolute values of the surface height deviations measured from the best fitting plane; Sz is the 10 point height over the surface, representing the average distance between the five highest peaks and five lowest valleys; Sdr is the developed area due to the surface texture versus an ideal plane area ratio; Sds is the summit densitym defining the number of peaks per unit area of the surface, Ssc is the mean summit curvature, indicating the shape and size of the higher areas of a surface Sc (core void volume) is the volume supported by the surface from 10–80% of the bearing ratio and Sv (surface void volume) is the volume the surface would support from 80% to 100% of the bearing ratio.

Composition

The molecular composition of representative abraded composite surfaces and their controls was evaluated by atenuated total reflection FTIR spectroscopy (ATR–FTIR). Randomly selected specimens (n = 10/product) were carefully debonded from the zirconia frames using a straight cutter plier with a torque motion, air-dried and the central regions facing the aligner were pressed via a sapphire anvil against a single-reflection diamond type IIa element (2 × 2 mm) of an ATR accessory (ZnSe lenses, 45^o incidence angle; Golden-Gate MKII, Specac, Oprington, Kent, UK) attached to an FTIR spectrometer (Spectrum GX, Perkin-Elmer, Buckinghamshire, Bacon, UK). Spectra were recorded under the following conditions: 4000–650 cm^{-1} wavenumber range, 4 cm^{-1} resolution, 20 scans co-addition and ~2 μm sampling depth at 1000 cm^{-1}. Furthermore, the degree of C=C bond conversion (DC%) of the attachments was measured employing spectra of unset restorative materials, obtained under the same conditions, as reference. The DC% was calculated based on the two-band technique according to the equation:

$$DC\% = 100 \times [1 \times (Ap_{(C=C)} \times Am_{(Ar)} / Am_{(C=C)} \times Ap_{(R)}]$$

where, A is the net peak absorbance height of the set (p) and unset (m) peaks of the methacrylate C=C bond stretching vibrations at 1636 cm^{-1} (analytical band; changes after photopolymerization) and R the aromatic (Ar) stretching vibrations at 1608 cm^{-1} (reference band; not affected by photo polymerization).

Statistical analysis

The roughness parameters and degree of C=C conversion values were tested for normality (Shapiro-Wilk test) and homoscedasticity (Brown-Forsythe test). For each property comparisons were made between controls (intact aligners) vs aligners after removal and re-seating. Moreover, comparisons between materials (conventional vs flowable composites) were registered. The level of statistical significance was pre-specified at a=0.05. All statistical analyses were performed with SigmaPlot v.14 software (Systat Software Inc., San Jose, CA, USA).

Results

Morphological features

Representative stereomicroscopic images of the zirconia frames with the composite attachments after removal and re-seating of the aligners are illustrated in Figure 1. The debonding rate in Group I (sculptable composite) was estimated as to 14.1% % whereas in Group 2 (flowable composite) as to 31.3%. Low magnification morphological features of Group I and II attachments bonded on various teeth for the two conditions (removed/reseated and control) are presented in Figures 2 and 3. The characteristic abrasion-induced defects by removal and re-seating of the aligners were scratches on the labial/buccal attachment free-surfaces, marginal defects mainly at the cervical regions with fracture or rounding of the attachment edges and angles, and in some cases loss of the characteristic surface texturing, which is mainly attributed to the topography of the aligner surfaces facing the teeth, due to the manufacturing process. The flowable composite (Group II) demonstrated higher frequency of texturing loss and bulk attachment fractures. The control groups (no removal/reseating of the aligners) demonstrated a textured surface morphology, with no marginal defects (Figure 4).

Figure 1. Stereomicroscopic images of zirconia frames with sculptable (Group I, upper row) and flowable (Group II, lower row) composite attachments after aligner placement and removal. Note more attachment failures in flowable (7.5× magnification, bar: 5mm)

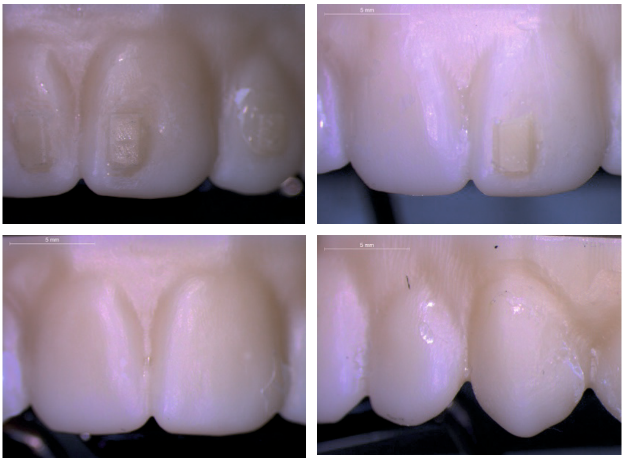


Figure 2. Stereomicroscopic images of zirconia frames with sculptable composite attachments (Group I) after aligner placement and removal. Note central surface scratches (a, d), marginal defects (b, e) and pronounced surface abrasion with loss of the characteristic surface texture (c, f). Right part of images: cervical region, left part: incisal region (25× magnification, bar: 1 mm).

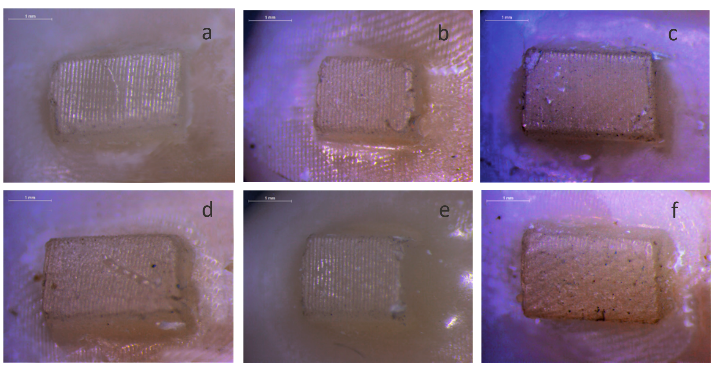


Figure 3. Stereomicroscopic images of zirconia frames with flowable composite attachments (Group II) after aligner placement and removal. Note central surface scratches (a, c, e, f), marginal defects (a, d, e, f), pronounced surface abrasion with loss of the characteristic surface texture (d, f) and bulk fractures (b). Right part of images: cervical region, left part: incisal region (25× magnification, bar: 1mm).

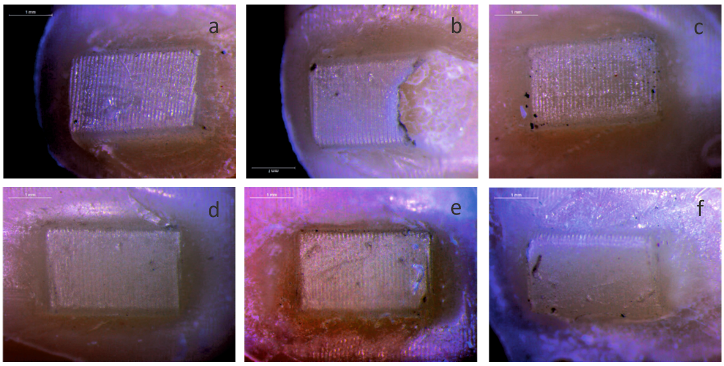
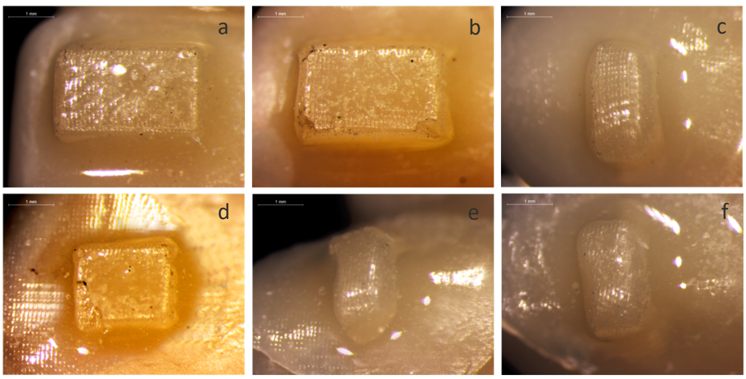


Figure 4. Stereomicroscopic images of zirconia frames with sculptable (Group I, upper row) and flowable (Group II, lower row) composite attachments of the control groups. In both groups the labial surfaces show the characteristic texturing, with minor marginal defects (25× magnification, bar: 1mm).



Roughness

3D-profilometric images of the regions used for roughness measurements are exhibited in Figures 5-8. The surfaces of the reference group of the sculptable composite attachments (Group I-control, Figure 5), demonstrated mild porosity (a, d) and protruding ridges corresponding to the texturing of the aligner surfaces facing the teeth (b). In few specimens severe porosity was identified at the central part of the attachments, associated with the texturing protrusions. After removal and reseating of the aligners (Group I, Figure 6), the sculptable composite surfaces exhibited well-defined protrusions attributed to aligner texturing, with evidence of abrasive wear and cracks. In some specimens deep abrasion tracks were located at the valleys and severely worn areas at the protruding composite ridges.

For the reference group of the flowable composite attachments (Group II-control, Figure 7), the patterns observed included smooth surfaces, surfaces with mild porosity allocated in line with mild texturing traces and a few cases of severe porosity and parallel fissures associated with the aligner texturing. After removal and reseating of the aligners (Group II, Figure 8), the flowable composite surfaces demonstrated excessive texturing protrusions with abraded peak ridges, cracks and severe abrasion in the valleys. In some specimens a generalized abrasion pattern was observed with pores, that completely modified the original surface profile.

Figure 5. 3D-profilometric images of the reference group of the sculptable composite attachments (Group I-control). The surfaces demonstrate mild porous defects (a, d), appearance of the texturing of the intaglio aligner surface (b) and in some cases severe porosity associated with the texturing protrusions (c) (10× magnification, 462.2 × 607.5 μm² analysis area).

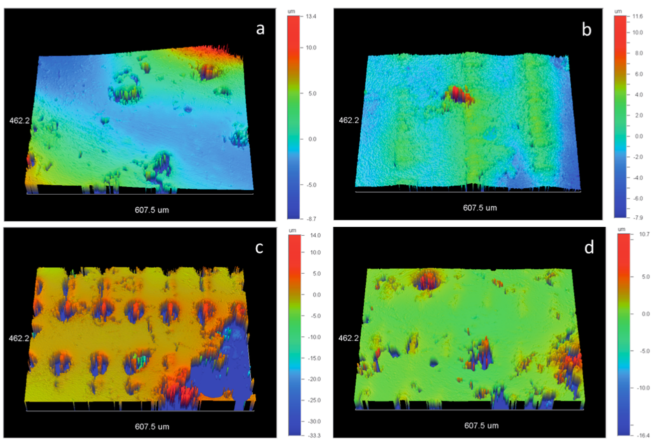


Figure 6. 3D-profilometric images of the group of the sculptable composite attachments after removal and reseating of the aligners (Group I). The surfaces demonstrate intense patterns of the aligner texturing with evidence of abrasive weas (b, c), cracks (a) and intensive abrasion tracks (d) at the texturing protrusions (10× magnification, 462.2 × 607.5 μm² analysis area).

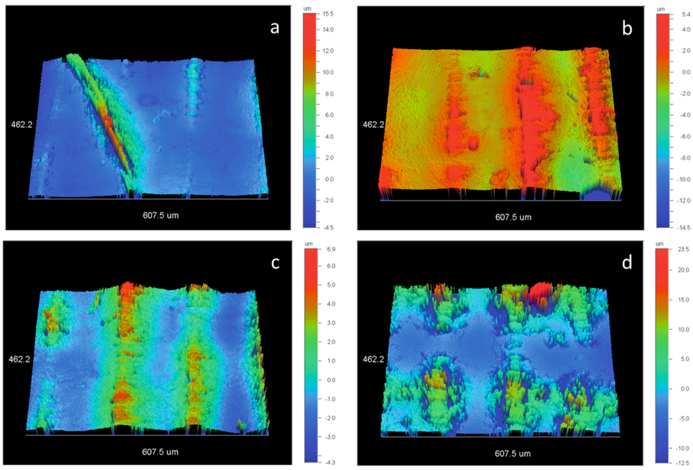


Figure 7. 3D-profilometric images of the reference group of the flowable composite attachments (Group II-control). Some surfaces demonstrate many porous defects and parallel fissures associated with the aligner texturing (a), whereas most were smooth (b, c) or with a mild porosity in line with the texturing (d) (10× magnification, 462.2 × 607.5 μm² analysis area).

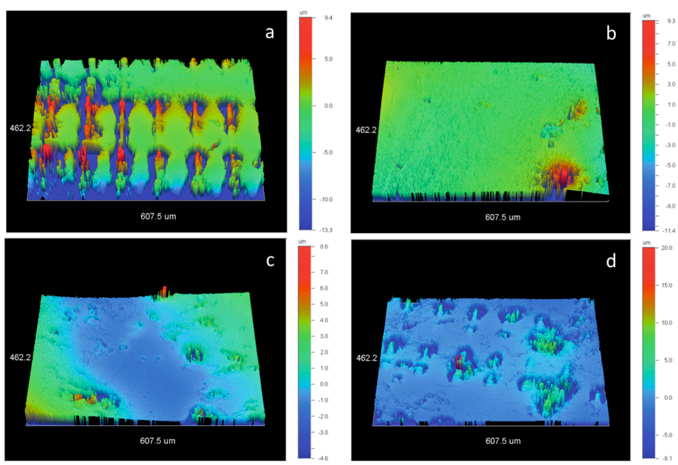
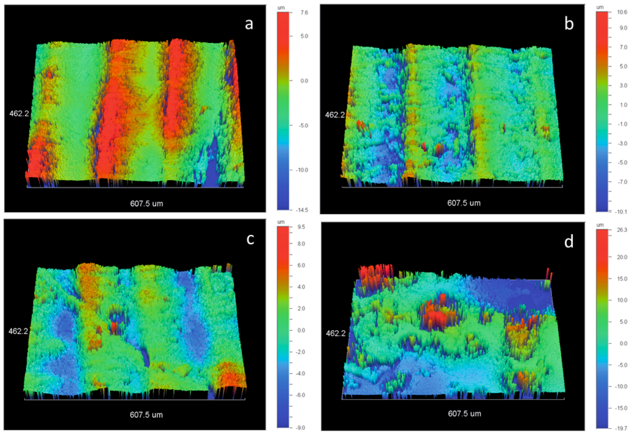


Figure 8. 3D-profilometric images of the flowable composite attachments after removal and reseating of the aligners (Group II). Most specimens demonstrated excessive texturing protrusions with abraded peak ridges and cracks (a), excessive abrasion in the valleys (b, c) and a generalized abrasion pattern with pores, which completely modified the texturing profile (d) (10× magnification, 462.2 × 607.5 μm² analysis area).



The results of the roughness parameter measurements are shown in Table 1. There were no statistically significant differences between the control group and the group with removal and reseating of the aligners per material (all comparisons non parametric with Mann-Whitney test, except for Sq, Sz, Sdr, Ssc in sculptable composite and Sdr, Ssc in flowable composite where Student's t-tests were used. Nevertheless, a marginal difference (p=0.054) was found in the Sc value in the flowable. Comparisons between the control materials demonstrated a statistically significant difference only in Sds in favour of the flowable (p=0.041), all comparisons Student's t-tests). Finally, comparisons between the two materials in the groups after removal and reseating of the aligners, showed a significantly lower Sds value in the sculptable composite group (p=0.047, all Mann-Whitney tests).

Table 1: The results of the roughness parameter measurements (means and standard deviations)

GROUP	Sa (μm)	Sq (μm)	Sz (μm)	Sc (μm3/mm2) ×103	Sv (mm3/mm2) ×103	Sdr (%)	Sds (1/mm2)	Ssc (1/mm)
I	2.064 (0.972)	2.747 (1.277)	1.877 (9.023)	3.59 (1.65)	0. 186 (0.081)	6.092 (4.351)	1760.853 (313.977) a	349.32 (123.001)
I Control	1.728 (1.184)	2.4997 (1.444)	18.514 (10.654)	2.45 (1.43)	0.287 (0.267)	3.278 (2.495)	1638.411 (397.592) A	245.168 (99.521)
II	1.973 (1.233)	2.562 (1.571)	17.715 (8.933)	3.14 (1.77)	0.200 (0.177)	5.148 (3.111)	2252.003 (931.144) a	373.42 (81.219)
II Control	1.363 (0.805)	1.7996 (1)	12.089 (4.306)	1.85 (0.951)	0.210 (0.151)	4.133 (2.021)	2119.904 (454.354) A	327.622 (104.81)

Same lowercase letters: Statistically significant differences for comparisons between materials after removal and reseating of aligners (Groups I-II, Mann-Whitney tests for all comparisons).
Same uppercase letters: Statistically significant differences for comparisons between control materials (Groups I Control)-II Control, Student's t-tests for all comparisons).

Composition

Full range ATR-FTIR spectra of unset and set specimens along with those subjected to aligner removal and reseating per material are presented in Figure 9. The spectra demonstrate characteristic peak assignments as follows (cm^{-1}): O–H (3442, 1140–1110), N–H (3371), aromatic C..C (3010, 1608, 1595,1510, 830, 801), $CH_3/CH_2/CH$ (2920–2880, 1465–1430, 1370–1360, 720–700), C=O (1715, 1320, 1290), C=C(1634, 1500, 895), CON–H (1540), C–O–C (1260, 1105–1000) and Si–O (1150–1000)[176]. These are the common peaks identified in composites with conventional bispenol-A adducts (i.e., BisGMA, BisEMA, BisPPMA) along with urethane dimethacrulate co-monomers (i.e., UDMA, DUDMA, etc). Based on manufacturer's information the flowable composite used contains in addition a cycloaliphatic monomer and an (β-allyl sulfone) addition fragmentation chain transfer (AFCT) reagent to reduce shrinkage stresses[6]. Some of the set materials of both material groups subjected to the repeated aligner removal and reseating cycles, showed strong peaks of water (3442 and 1642 cm^{-1}), which were not reduced by the conventional drying methods used for all specimens, implying that this water fraction is strongly absorbed.

Figure 9. ATR-FTIR spectra of unset and set states of the sculptable (left) and flowable (right) composite materials used as aligner attachments. SETR1 and 2 correspond to specimens subjected to repeated removal and reseating aligner cycles. Arrows show the strong peaks of strongly bound water observed in some specimens (4000-650 cm^{-1} wavenumber range, absorbance scale).

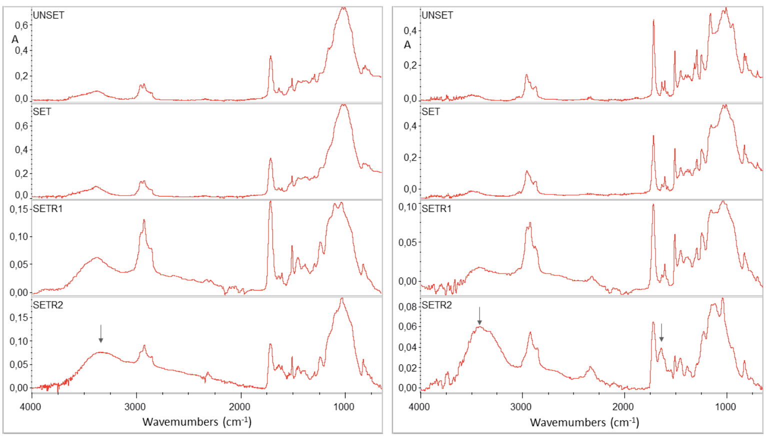


Figure 10 illustrates representative expanded spectra used for calculation of the degree of C=C conversion measurements (DC%), along with the annotation of the analytical and reference bands. Table 2 summarizes the results of DC% for the groups tested. Comparisons between the control group and the group with removal and reseating of the aligners per material, between the control groups and between the material groups with removal and reseating of the aligners showed statistically insignificant differences ($p>0.05$, all Student's t-tests).

Figure 10. Expanded ATR-FTIR spectra of unset and set states of the sculptable (left) and flowable (right) composite materials used as aligner attachments. SETR1 and 2 correspond to specimens subjected to repeated removal and reseating aligner cycles. C=C, Ar denote the peaks of analytical and reference bands respectively used for calculation of the DC% (1670-1570 cm^{-1} wavenumber range, absorbance scale).

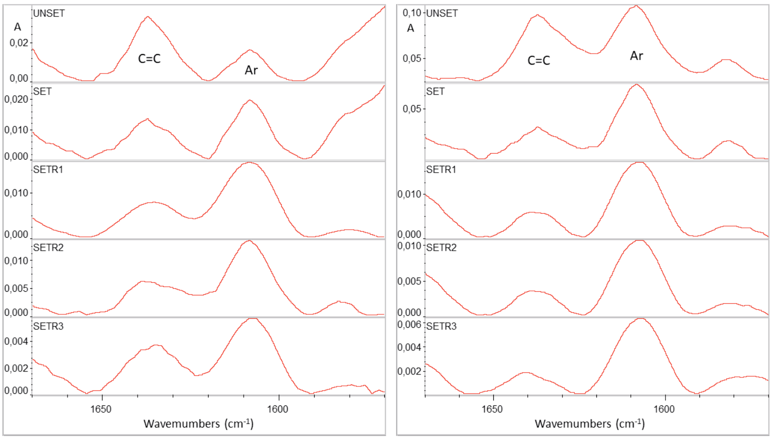


Table 2: The results of DC% measurements (means and standard deviations).

GROUP	DC (%)
I	69.7 (8.8)
I Control	62.6 (1.9)
II	66.2 (4.8)
II Control	61.5 (1.1)

Discussion

The results of the present experimental study showed that there were no statistically significant differences in the roughness parameters and DC% between the control and the group of attachments after removal and reseating, for the sculptable and flowable composites respectively. Therefore, the null hypothesis should be accepted. Statistically significant differences were found only in Sds when comparisons were made between the two materials for the control or the removal and reseating states.

The materials selected were a sculptable universal and a flowable universal restoratives, which are the types of the composites used for aligner attachments. These materials are based in similar monomer systems (BisGMA, BisEMA, UDMA) with the addition of dicyclodecane dimethanol dimethacrylate (DCDDMA) in the later. The sculptable composite demonstrates higher viscosity and a “putty” consistency, whereas the second is a thixotropic flowable. The sculptable has a higher filler content (75-76w%, 53-55% v%) than the flowable (68.2 w%, 46.4 v%) and better mechanical properties. Although in previous studies high loaded sculptable materials were used[5,7] for aligner attachments, currently several manufacturers have introduced flowable materials. The main reason is the improved rheological characteristics of the flowables, which could facilitate easy and porous-free resin penetration into the attachment frame of the aligners and contact with tooth surfaces. For this issue the putty consistency of sculptable composites may increase porosity when applied in the box-shaped inclusions of the aligners due to inclusion of air. Moreover, the reduced wettability of sculptables on tooth surfaces may further promote porosity at the tooth-attachment interface.

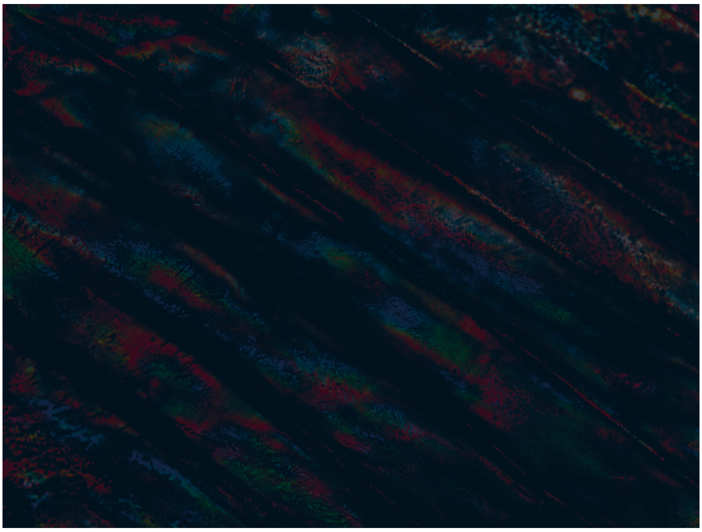
In the present study the substrates used for bonding the attachments were Zirconia (3Y-TZP) arches. The reason for the selection of this material was that the original design of the study included the assessment of the water eluents from the composite attachments, which currently is in the final stage of measurements employing liquid chromatography and mass spectrometry (LC-MS). The selection of zirconia arches was based on the water insolubility, absence of release of interfering compound in the LC-MS measurements, dimensional stability in water and the bonding capacity of the composite attachments. The zirconia surfaces were sandblasted with 50 μm alumina with an intraoral sandblaster at low-pressure and treated with a universal primer containing two phosphate monomers (10-MDP, MDTP). The use of alumina blasting with phosphate-monomer containing primers has been widely accepted as an efficient treatment method of the intaglio surfaces of zirconia crowns for strong and durable bonding with composite luting agents, by combining micromechanical retention and chemical adhesion[8,9]. The study was limited to one week period to provide information on the early changes induced in the attachments after bonding and aligner placement, within the effective service period of an aligner. This initial in-service period is the most important since the attachments are not matured in terms of polymerization and are directly exposed in the water along with the extra-coronal forces induced by the aligner, which produce an abrasive effect on the original material morphology and topography. Note that a week of water immersion is considered as a conventional water absorption equilibration period, where remaining monomer and early oxidative compounds of pendant C=C bonds are released[10]. The rate of these phenomena is usually reduced with time, especially when the abraded attachments loose conformity with the aligners and thus the aligner-attachment interfacial friction is reduced[5].

The stereomicroscopic and the optical profilometric roughness measurements were performed on attachments bonded to the frames, to avoid debonding induced defects. The stereomicroscopic assessment of the morphological features of the control groups demonstrated a few problems in integrity of the buccal angles of the sculptable material, possibly assigned to air inclusion. Moreover, there was evidence of surface porosity and loss of the characteristic surface texture of the intaglio aligner surface in some specimens, which may indicate inadequate wettability of the aligner by the sculptable composite. Due to the better wettability of the aligner surfaces, such defects were limited in the flowable, although still some evidence of labial surface defects were registered. In the groups subjected to the repeated cycles of attachment loading, after aligner removal and reseating, the attachment surfaces exhibited abrasion-induced morphological changes, such as cracks, angle rounding, loss of surface texturing and some cases of bulk fractures. Scratches and bulk fractures were more frequently observed in the flowable composite, a finding mainly attributed to the lower mechanical properties of this material. An interesting finding was the increased debonding percentage found in the flowable group. More than half of this percentage was associated with debonding during the first removal of the aligner, with the attachment locked inside the aligner frame. Two possible reasons may be implicated with this phenomenon; first the higher wettability of the aligner by the flowable material and second the higher mechanical retention of the flowable with the textured surface due to the higher volumetric shrinkage of the flowable from the composite (1.83

vs 3.21%[11,12]) within a complex three-dimensional retentive structure than the tooth surface. It should be noted that in the present study the bonding treatments to zirconia were the same, for materials with small differences in the monomer content and that the specific flowable material was selected based on the manufacturer's claim for low shrinkage. Although the clinical relevance of this finding is unknown, it may indicate a potential limitation of the currently available flowable composite materials as aligner attachments. Nevertheless, sculptable composites may demonstrate application problems in very small aligner cavities. A hydrophobic low-flow consistency materials could present handling advantages in such cases.

The roughness analysis was used to quantify the topographic differences between the control specimens and the specimens after aligner removal and reseating. Amplitude, hybrid and functional parameters were selected for better characterization of the surfaces. From all these parameter Sdr and Ssc are considered as of major importance to characterize how surfaces interact when the one is moved against the other, how friction is implicated and how they will abrade due to the contact. These two parameters focus on the actual contact area due to the presence of surface summits than the entire area and can be used to predict the mode of surface deformation under load, the friction and wear characteristics of a surface[13]. The data used for roughness parameters were unfiltered incorporating the waveness pattern of the attachments produced by the intaglio aligner surface texturing (Figure 11). The 3D-profilometric images obtained at 10× nominal magnification of the Mirau lens were more than twice the magnification of the stereomicroscope, with each image representing the most affected zone. The porosity observed in the control groups was more pronounced in the sculptable composite. This is in accordance with the wetting problems and the air inclusion found also in the stereomicroscopic images. However, in few cases of both control groups, excessive porosity aligned with texturing traces was observed, with more intense characteristics in the flowable material. A possible explanation is inadequate wetting at the region with inclusion of air voids (spherical, ellipsoid), which after setting created larger defects in the flowable material, due to its higher shrinkage. After aligner removal and reseating the sculptable material presented various degrees of abrasion of the protruding regions. In some cases of the flowable material a generalized surface wear was observed by completely removing the parent morphological features of the control group, suggesting a more severe effect. The high variances in the topography resulted in statistically insignificant values between all paired comparisons (control attachments vs attachments after aligner removal and replacement for both materials), with a marginal difference found only in the flowable for Sds ($p=0.054$). This may indicate that the number of protruding summits were reduced per surface area after aligner removal and reseating. Comparison between the control materials and the materials after aligner replacement and reseating, clearly demonstrated a significantly higher Sds for the flowable. This finding corroborates the improved rheological properties of the flowable, which may penetrate more efficiently into the texturing details of the aligner surfaces facing the teeth.

Figure 11. Reflected polarized light image of the inner surface of the aligner, with the characteristic texturing.



The analysis of the composition was mainly limited to the organic part of the composites, since the organic compounds released are mainly associated with possible side effects. The ATR-FTIR spectroscopic analysis probed the superficial 2 μm zone of the materials, which is within the range of the Sa values of all the groups tested. The spectra of the materials after control and aligner removal/reseating demonstrated similar peaks, indicating no evidence of hydrolytic changes. This may be explained by the short water-immersion period and the limited removal and reseating cycles. Moreover, the similar spectra of the worn surfaces with the control indicate that the remaining solid material was not subjected to other structural changes, except for some strong contributions of absorbed water. This water fraction should be strongly bound in the superficial material region, since it was not removed by conventional air-drying, and may increase the hydrolytic susceptibility of the materials. The degree of C=C conversion is a fundamental property for the methacrylate-based dental polymers, as it is related to many mechanical, chemical and biological properties of these materials[14]. The DC% values recorded did not show statistically significant differences between the control and the aligner removal/reseating groups per material or between the materials for the same conditions. The conversion ranged between 61.5-69.7%, which is above the limits for composite restorative materials offering an acceptable abrasive wear depth (~55%)[15].

The results of the present in-vitro study showed that a flowable material was more affected by aligner removal and replacement that a sculptable composite analogue, even in one-week testing period in water. The main issues raised were the higher failure ratio of flowable attachments and the more severe surface deterioration in specimens demonstrating major surface defects. Although the study was performed on zirconia arches, to allow further evaluation of the composite materials eluents, the comparative laboratory conditions employed may establish the need for further studies to elucidate the effects of attachment-aligner interfacial interactions. The loss in attachment-aligner conformity, which may affect the biomechanics of the treatment, the attachment surface roughness in relation to plaque retention capacity, the chemical stability of the worn surfaces and the polymer degradation adducts released are some topics seeking further research to establish the efficiency and safety of the treatment outcome.

Conclusion

Characteristic abrasion-induced defects by removal and reseating of the aligners were detected without significant changes in the roughness parameters (control-tested), but with significant higher values in Sdr between materials within control or tested groups. The sculptable material appeared superior in terms of morphology and retention characteristics. Insignificant differences in the C=C conversion were found in the groups tested. However, in some specimens strong peaks or irreversibly absorbed water were detected indicating hydrolytic susceptibility of the superficial composite zone.

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